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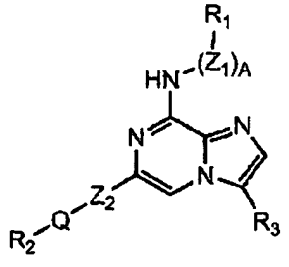
(54) Title: CERTAIN IMIDAZO[1,2-a]PYRAZIN-8-YLAMINES, METHOD OF MAKING, AND METHOD OF USE THEREOF



(1)

(57) Abstract: At least one chemical entity chosen from compounds of Formula (1) and pharmaceutically acceptable pharmaceutically acceptable salts, hydrates, solvates, crystal forms, diastereomers, and prodrugs thereof. Methods of treating or preventing disorders in which aberrant kinase activity is implicated, pharmaceutical compositions, and methods for detecting the presence kinases in cells or biological preparations and for identifying kinases of therapeutic interest.

Certain Imidazo[1,2-a]pyrazin-8-ylamines, Method of Making, and Method of Use Thereof

[0001] This application claims priority to U.S. provisional application 60/519,311 filed November 11, 2003.

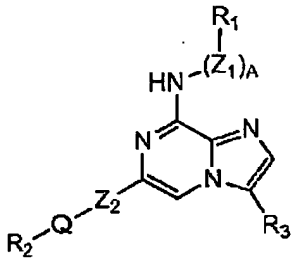
[0002] Provided herein are certain imidazo[1,2-a]pyrazinylamines and related compounds, compositions comprising such compounds, and methods of their use.

[0003] One of the central post-translational control elements in eukaryotic signal transduction is the phosphorylation of the hydroxyl moiety of serine, threonine, or tyrosine. The phosphorylation state of a given protein can govern its enzyme activity, stability, protein-protein binding interactions, and cellular distribution. Phosphorylation and dephosphorylation is thus a "chemical switch" that allows the cell to transmit signals from the plasma membrane to the nucleus, and to ultimately control gene expression. Kinases are involved in the control of cell metabolism, growth, differentiation, and apoptosis. Kinase signaling mechanisms have been implicated in the onset of cancer, metabolic disorders (for example diabetes), inflammation, immune system disorders, and neurodegeneration. Certain kinases have been implicated in cell proliferation and carcinogenesis. For example, many human cancers are caused by disregulation of a normal protein (e.g., when a proto-oncogene is converted to an oncogene through a gene translocation).

[0004] Inhibitors of kinases are among the most important pharmaceutical compounds known. Serine/threonine kinase inhibitors are also pharmaceutically important. For example, inhibitors of protein kinase C beta are known to be useful for treatment of diabetic macular edema and diabetic retinopathy. An inhibitor of cyclin-dependent kinases, is under development for treatment of mantle cell lymphoma (MCL) and fludar refractory chronic lymphocytic leukemia (CLL). One Raf kinase inhibitor is in development for treatment of solid tumors and myeloid leukemia, and another is being investigated for treatment of ovarian cancer. Several p38 mitogen-activated protein kinase inhibitors have been investigated for treatment of inflammation, rheumatoid arthritis, and myelodysplastic syndrome (MDS).

[0005] Modulators of kinase activity which may generally be described as imidazo[1,2-a]pyrazinylamines are provided herein. Certain compounds provided herein are inhibitors of angiogenic and/or oncogenic kinases.

[0006] In certain embodiment the invention provides at least one chemical entity chosen from compounds of Formula I:

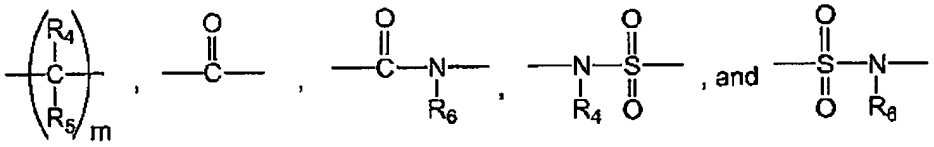


(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo;

m is chosen from 0, 1, 2, and 3; and

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from

hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are indcpendently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-

C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

phenylene,

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6

alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

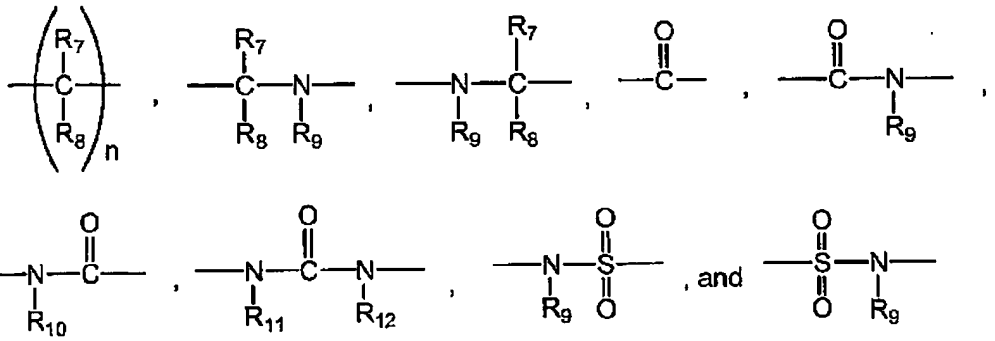
pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

naphthylidene, and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo;

n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, carboxy, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, carboxy, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6

haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl.

[0007] In certain embodiments, the invention provides a pharmaceutical composition comprising at least one chemical entity described herein, and at least one pharmaceutically acceptable carrier or excipient.

[0008] In certain embodiments, the invention provides methods of treating a kinase-implicated condition in a mammal having a kinase-implicated condition, comprising administering to the mammal a therapeutically effective amount of at least one chemical entity described herein.

[0009] In certain embodiments, the invention provides methods of treating cancer, comprising administering to a mammal in need thereof a therapeutically

effective amount of at least one chemical entity described herein. In some embodiments, a therapeutically effective amount of at least one other antitumor therapeutic is also administered.

[0010] In certain embodiments, the invention provides methods for identifying a kinase, comprising contacting an organism, cell, or preparation comprising the kinase with at least one chemical entity described herein, and detecting modulation of an activity of the kinase.

[0011] In certain embodiments, the invention provides methods of treating a Btk-implicated condition in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one chemical entity described herein.

[0012] In certain embodiments, the invention provides methods for identifying Btk, comprising contacting an organism, cell, or preparation comprising the kinase with at least one chemical entity described herein.

[0013] In certain embodiments, the invention provides methods of treating a Btk-implicated autoimmune/inflammatory condition in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one chemical entity described herein.

[0014] FIGURE 1 is a schematic illustrating one synthesis of the present compounds.

[0015] FIGURE 2 is a schematic illustrating another synthesis of the present compounds.

[0016] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise. The following abbreviations and terms have the indicated meanings throughout:

[0017] As used herein, when any variable occurs more than one time in a chemical formula, its definition on each occurrence is independent of its definition at every other occurrence. In accordance with the usual meaning of "a" and "the" in patents, reference to "a" kinase or "the" kinase is inclusive of one or more kinases. Unless otherwise specified the terms "compound" and "compounds" include all

pharmaceutically acceptable forms of the disclosed structures, salts, hydrates, solvates, prodrugs, and the like.

[0018] Formula I includes all subformulae described herein.

[0019] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom.

[0020] By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

[0021] "Alkyl" encompasses straight chain and branched chain having the indicated number of carbon atoms. For example C_1-C_6alkyl encompasses both straight and branched chain alkyl of from 1 to about 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl, and the like. Alkylene is another subset of alkyl, referring to the same residues as alkyl, but having two points of attachment. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, "butyl" is meant to include n-butyl, sec-butyl, isobutyl and t-butyl; "propyl" includes n-propyl and isopropyl.

[0022] "Cycloalkyl" indicates a saturated hydrocarbon ring group, having the specified number of carbon atoms, usually from 3 to about 7 ring carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl as well as bridged and caged saturated ring groups such as norbornane.

[0023] By "alkoxy" is meant an alkyl group of the indicated number of carbon atoms attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy,

isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. In certain embodiments, alkoxy groups herein are C_1-C_4alkoxy groups.

[0024] "Mono- and di-alkylcarboxamide" encompasses a group of the formula $-(C=O)NR_aR_b$ where R_a and R_b are independently chosen from hydrogen and alkyl groups of the indicated number of carbon atoms, provided that R_a and R_b are not both hydrogen.

[0025] By "alkylthio" is meant an alkyl group of the indicated number of carbon atoms attached through a sulfur bridge.

[0026] "Alkanoyl" refers to an ester group of the formula $-OC(O)(C_2$-C_6 alkyl) attached through the ester oxygen.

[0027] By "alkoxycarbonyl" is meant an ester group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a C_1-C_6alkoxycarbony group is an alkoxy group having from 1 to about 6 carbon atoms attached through its oxygen to a carbonyl linker.

[0028] By "amido" is meant $-NH(C=O)R$, wherein the R group is chosen from hydrogen and C_1-C_7alkyl. "Amido" also includes $-(C=O)NRR$, wherein each R is chosen from hydrogen and C_1-C_7alkyl. Except when R is hydrogen, each R may be unsubstituted or substituted with one or more, such as one, two or three, substituents independently chosen from halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino.

[0029] By "amino" is meant the group $-NH_2$.

[0030] "Mono- and di-(alkyl)amino" encompasses secondary and tertiary alkyl amino groups, wherein the alkyl groups are as defined above and have the indicated number of carbon atoms. The point of attachment of the alkylamino group is on the nitrogen. Examples of mono- and di-alkylamino groups include ethylamino, dimethylamino, and methyl-propyl-amino.

[0031] "Mono- and di-(alkyl)aminoalkyl" encompasses mono- and di-(alkyl)amino as defined above linked to an alkyl group.

[0032] By "amino(alkyl)" is meant an amino group linked to an alkyl group having the indicated number of carbons. Similarly "hydroxyalkyl" is a hydroxy group

linked to an alkyl group.

[0033] "Aryl" encompasses:

5- and 6-membered carbocyclic aromatic rings, for example, benzene;

bicyclic 9- and 10-membered ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and tetralin; and

tricyclic 12- to 14-membered ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

For example, aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms chosen from N, O, and S. Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene.

[0034] The term "aryloxy" refers to the group -O-aryl.

[0035] The term "carboxy" refers to the group –C(O)OH.

[0036] The term "halo" includes fluoro, chloro, bromo, and iodo, and the term "halogen" includes fluorine, chlorine, bromine, and iodine.

[0037] "Haloalkyl" indicates alkyl as defined above having the specified number of carbon atoms, substituted with 1 or more halogen atoms, generally up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0038] "Heteroaryl" encompasses:

5- to 7-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and

7- to 10-membered bicyclic heterocyclic rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring.

For example, heteroaryl includes 5- to 7-membered heterocycloalkyl, aromatic rings fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings contains one or more heteroatoms, the point of attachment may be at the heteroaromatic ring or the cycloalkyl ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In certain embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In certain embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, systems (as numbered from the linkage position assigned priority 1), such as 2-pyridyl, 3-pyridyl, 4-pyridyl, 2,3-pyrazinyl, 3,4-pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,3-pyrazolinyl, 2,4-imidazolinyl, isoxazolinyl, oxazolinyl, thiazolinyl, thiadiazolinyl, tetrazolyl, thienyl, benzothiophenyl, furanyl, benzofuranyl, benzoimidazolinyl, indolinyl, pyridizinyl, triazolyl, quinolinyl, pyrazolyl, and 5,6,7,8-tetrahydroisoquinoline. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a pyridyl group with two points of attachment is a pyridylidene.

[0039] In the term "heteroarylalkyl," heteroaryl and alkyl are as defined herein, and the point of attachment is on the alkyl group. This term encompasses, but is not limited to, pyridylmethyl, thiophenylmethyl, and (pyrrolyl)1-ethyl.

[0040] By "heterocycloalkyl" is meant a single aliphatic ring containing at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, and the like, as well as combinations comprising at least one of the foregoing heteroatoms. Suitable heterocycloalkyl groups include, for example (as numbered from the linkage position assigned priority 1), 2-pyrrolinyl,

2,4-imidazolidinyl, 2,3-pyrazolidinyl, 2-piperidyl, 3-piperidyl, 4-piperdyl, and 2,5-piperzinyl. Morpholinyl groups are also contemplated, including 2-morpholinyl and 3-morpholinyl (numbered wherein the oxygen is assigned priority 1).

[0041] As used herein, "modulation" refers to a change in kinase activity as a direct or indirect response to the presence of compounds of Formula 1, relative to the activity of the kinase in the absence of the compound. The change may be an increase in activity or a decrease in activity, and may be due to the direct interaction of the compound with the kinase, or due to the interaction of the compound with one or more other factors that in turn affect kinase activity. For example, the presence of the compound may, for example, increase or decrease kinase activity by directly binding to the kinase, by causing (directly or indirectly) another factor to increase or decrease the kinase activity, or by (directly or indirectly) increasing or decreasing the amount of kinase present in the cell or organism.

[0042] By "piperazinyl" is meant unsubstituted piperazine, as well as piperazines independently substituted on 1-4 carbon atoms with at least one substituent chosen from hydroxy, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), and sulfonamido.

[0043] By "sulfonamido" is meant -$S(O)_2N$- in either S-linked (-$S(O)_2NRR$) or N-linked orientation –$NS(O)_2RR$ orientation, wherein each R may be independently chosen from hydrogen and C_1-C_7alkyl wherein alkyl is as defined above, such as 3- to 7-membered cycloalkyl, and heterocycloalkyl rings. When R is not hydrogen, each R may be unsubstituted or substituted with one or more, such as one, two or three, substituents independently chosen from, e.g., halo, C_1-C_6alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_6 alkyl)amino, and di-(C_1-C_6 alkyl)amino.

[0044] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo (i.e., =O) then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation into an effective therapeutic agent. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion.

[0045] If the compounds of Formula I have asymmetric centers, then Formula I includes all of the optical isomers and mixtures thereof. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included. Those compounds can be, for example, racemates or optically active forms. In those situations, the single enantiomers or diastereomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high-pressure liquid chromatography (HPLC) column. Where compounds of Formula I exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers, and includes all tautomeric forms of the compound.

[0046] Chemical entities of the present invention include, but are not limited to, compounds of Formula I and all pharmaceutically acceptable forms thereof. Pharmaceutically acceptable forms of the compounds recited herein include pharmaceutically acceptable salts, hydrates, solvates, crystal forms, polymorphs, chelates, non-covalent complexes, esters, clathrates, prodrugs, and mixtures of such compounds. In certain embodiments, the compounds described herein are in the form of pharmaceutically acceptable salts. Hence, the terms "chemical entity" and "chemical entities" also encompass pharmaceutically acceptable salts, hydrates, solvates, crystal forms, polymorphs, chelates, non-covalent complexes, esters, clathrates, prodrugs, and mixtures of such compounds.

[0047] "Pharmaceutically acceptable salts" include, but are not limited to salts

with inorganic acids, such as hydrochlorate, phosphate, diphosphate, hydrobromate, sulfate, sulfinate, nitrate, and like salts; as well as salts with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate such as acetate, HOOC-$(CH_2)_n$-COOH where n is 0-4, and like salts. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium, and ammonium.

[0048] In addition, if the compound of Formula I is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts encompassed by Formula I.

[0049] As noted above, prodrugs also fall within the scope of chemical entities, for example acylated prodrugs of the compounds of Formula I. The term "prodrugs" includes any compounds that become compounds of Formula I when administered to a patient, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate and like derivatives of functional groups (such as alcohol or amine groups) in the compounds of Formula I.

[0050] The term "solvate" refers to the compound formed by the interaction of a solvent and a compound. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates.

[0051] The term "active agent" is used to indicate a chemical entity which has biological activity. In certain embodiments, an "active agent" is a compound having pharmaceutical utility. For example an active agent may be an anti-cancer therapeutic.

[0052] "Treatment or treating means any treatment of a disease in a patient,

including:

a) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;

b) inhibiting the disease;

c) slowing or arresting the development of clinical symptoms; and/or

d) relieving the disease, that is, causing the regression of clinical symptoms.

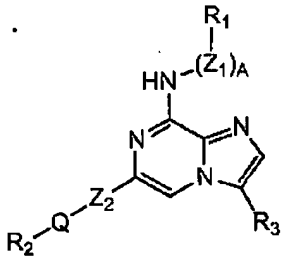
[0053] "Diseases or disorders responsive to kinase modulation" refer to pathologic conditions that depend, at least in part, on the activity of one or more protein kinases, for example, angiogenic kinases and/or oncogenic kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including cell proliferation, differentiation, and invasion. Diseases or disorders responsive to kinase modulation include but are not limited to psoriasis, cancer (for example, chronic myelogenous leukemia, gastrointestinal stromal tumors, non-small cell lung cancer, breast cancer, ovarian cancer, recurrent ovarian cancer, prostate cancer such as hormonal refractory prostate cancer, kidney cancer, head and neck cancer, or colorectal cancer), immunoregulation (graft rejection), atherosclerosis, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, diabetes (for example insulin resistance or diabetic retinopathy), septic shock, and the like.

[0054] "Patient" refers to an animal, such as a mammal, for example a human, that has been or will be the object of treatment, observation or experiment. The methods of the invention can be useful in both human therapy and veterinary applications. In some embodiments, the patient is a mammal, and in some embodiments the patient is human.

[0055] The term "therapeutically effective amount" of a chemical entity of this invention means an amount effective, when administered to a human or non- human patient, to provide a therapeutic benefit such as an amelioration of symptoms, e.g., an amount effective to at least decrease the symptoms of a disease or disorder responsive to kinase modulation, including those diseases and disorders response to modulation of ephrin receptors, such as ephrin B receptors, and including EphB4, and, in certain

embodiments, an amount sufficient to reduce cancer symptoms, decrease the number of detectable cancerous cells in an organism, detectably slow or stop the growth of a cancerous tumor, or, in certain embodiments, to shrink a cancerous tumor. In certain circumstances a patient suffering from cancer may not present symptoms of being affected. Thus a therapeutically effective amount of a compound is also an amount sufficient to prevent a significant increase or significantly reduce the detectable level of cancerous cells or cancer markers in the patient's blood, serum, or tissues. A significant increase or reduction in the detectable level of cancerous cells or cancer markers is any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student's T-test, where $p < 0.05$.

[0056] Within certain embodiments, the invention provides at least one chemical entity chosen from compounds of Formula I:

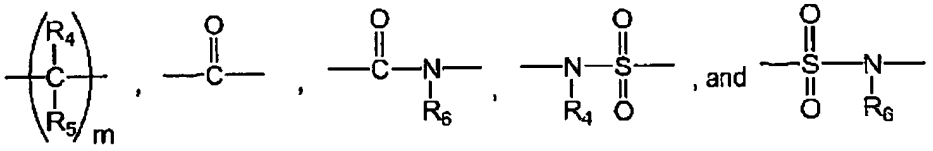


(Formula I)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

phenylene,

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

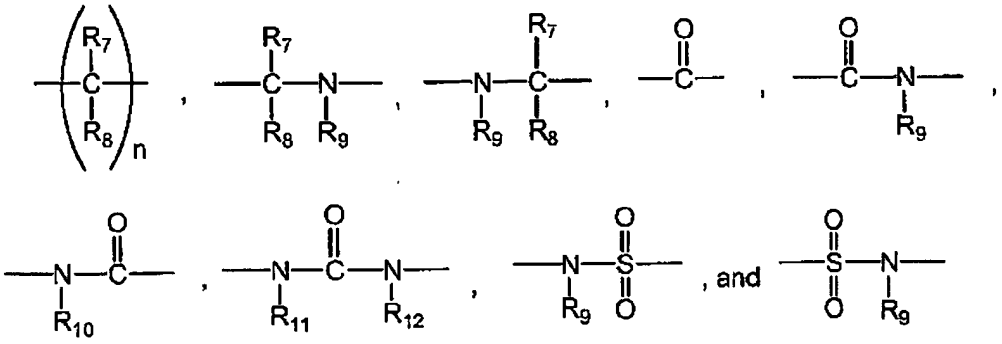
pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

naphthylidene, and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo; and n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-

C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

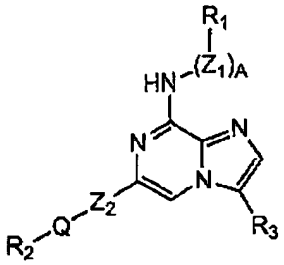
substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl.

[0057] Within certain embodiments, the invention provides at least one chemical entity chosen from compounds of Formula I:

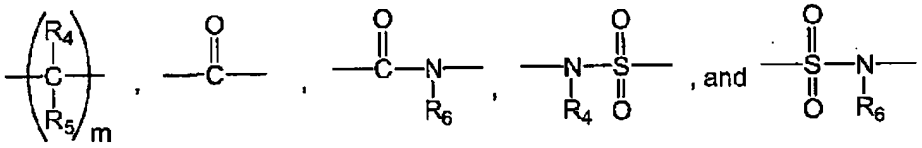


(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

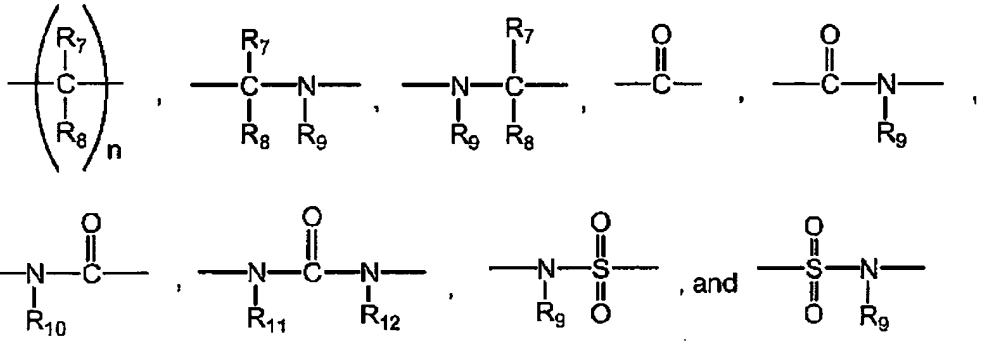
pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2

haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl), and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo; and n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen

from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

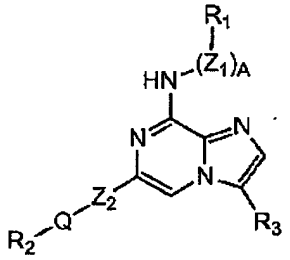
C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl.

[0058] Within certain embodiments, the invention provides at least one chemical entity chosen from compounds of Formula I:

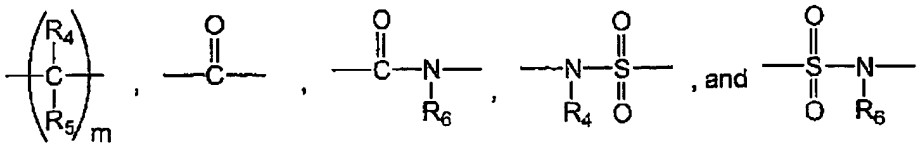


(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_1 is chosen from

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, and

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6

haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

phenylene,

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

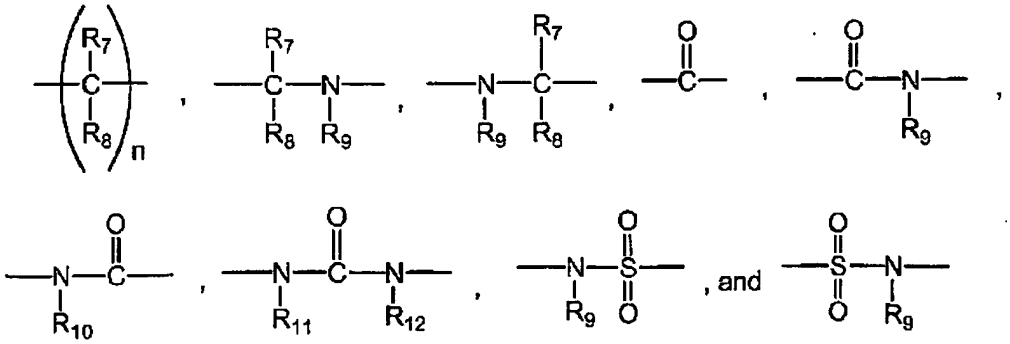
pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

naphthylidene, and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo; and n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

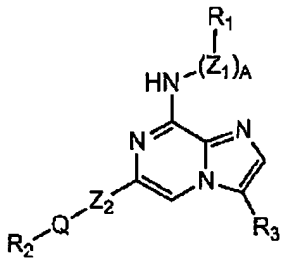
substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl.

[0059] Within certain embodiments, the invention provides at least one chemical entity chosen from compounds of Formula I:

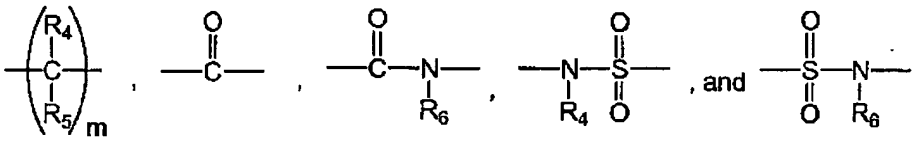


(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

phenylene,

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

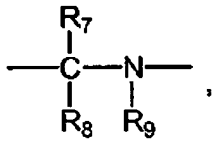
pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2

haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

naphthylidene, and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

Q is  ,

wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo; and n is chosen from 0, 1, 2, and 3; and

R_9 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro,

cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

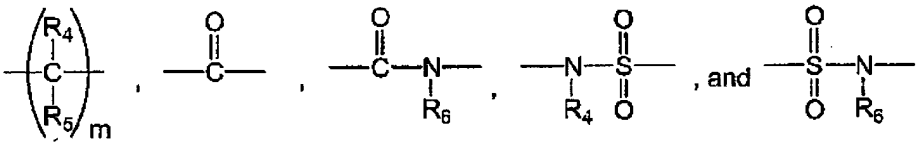
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl.

[0060] When referring to compounds of Formula I, in some embodiments, A is chosen from 0 and 1; and

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo; and m is chosen from 0, 1, 2, and 3; and

R_6 is chosen from

hydrogen,

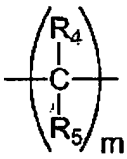
C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl), heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl).

In some embodiments, R_6 is chosen from hydrogen, C_1-C_6 alkyl, and phenyl. In some embodiments, A is 0 and Z_1 is absent. In some embodiments, A is 1 and Z_1 is



wherein R_4 and R_5 are independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo; and m is chosen from 0, 1, 2, and 3. In some embodiments, R_4 and R_5 are hydrogen; and m is chosen from 0, 1, 2, and 3. In some embodiments, R_4 and R_5 are hydrogen; and m is chosen from 1, 2, and 3. In some embodiments, R_4 and R_5 are hydrogen; and m is chosen from 0 and 1. In some embodiments, R_4 and R_5 are hydrogen; and m is 1.

[0061] When referring to compounds of Formula I, in some embodiments, R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl. In some embodiments, R_3 is hydrogen.

[0062] When referring to compounds of Formula I, in some embodiments, R_1 is chosen from

hydrogen,
C_1-C_7 alkyl,
C_1-C_6 alkoxy,
C_3-C_7 cycloalkyl,
(C_3-C_7 cycloalkyl)methyl,
heterocycloalkyl,
(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro,

cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

[0063] When referring to compounds of Formula I, in some embodiments, R_1 is chosen from

C_3-C_7 cycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di- (C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

[0064] When referring to compounds of Formula I, in some embodiments, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl,

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyrimidinyl, and

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyrimidinyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

[0065] When referring to compounds of Formula I, in some embodiments, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

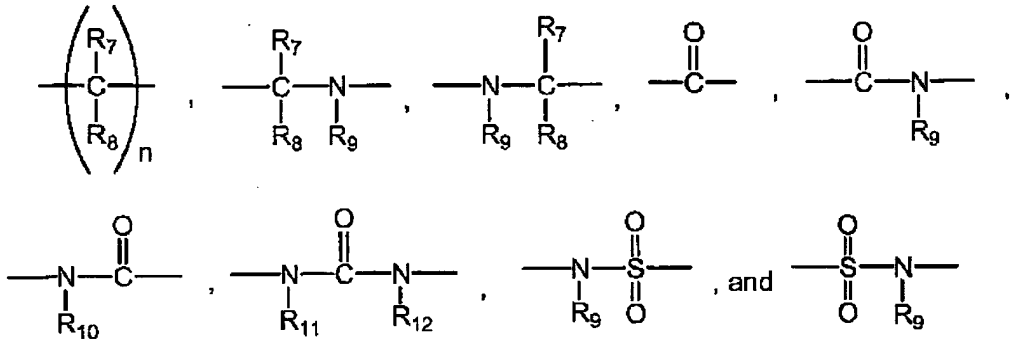
substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6

alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6 alkoxycarbonyl.

[0066] When referring to compounds of Formula I, in some embodiments, Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo;

n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro,

cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl).

When referring to compounds of Formula I, in some embodiments, each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo; and n is chosen from 1 and 2. In some embodiments, R_9-R_{12} are each independently chosen from hydrogen, C_1-C_6 alkyl, and phenyl.

[0067] When referring to compounds of Formula I, in some embodiments, Z_2 is chosen from

phenylene,

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

naphthylidene, and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

[0068] When referring to compounds of Formula I, in some embodiments, Z_2 is chosen from

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

[0069] When referring to compounds of Formula I, in some embodiments, Z_2 is chosen from

phenylene,

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

pyridylidene, and

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

[0070] When referring to compounds of Formula I, in some embodiments, Z_2 is

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

[0071] When referring to compounds of Formula I, in some embodiments, R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy,

C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl.

[0072] When referring to compounds of Formula I, in some embodiments, R_2 is chosen from

(C_3-C_7 cycloalkyl)methyl,

substituted (C_3-C_7 cycloalkyl)methyl chosen from mono-, di-, and tri-substituted (C_3-C_7 cycloalkyl)methyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

substituted (heterocycloalkyl)C_1-C_2 alkyl chosen from mono-, di-, and tri-substituted (heterocycloalkyl)C_1-C_2 alkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7

cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy, and

substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl.

[0073] When referring to compounds of Formula I, in some embodiments, R_2 is chosen from

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

(C_3-C_7 cycloalkyl)methyl,

substituted (C_3-C_7 cycloalkyl)methyl chosen from mono-, di-, and tri-substituted (C_3-C_7 cycloalkyl)methyl wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents

are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

(heterocycloalkyl)C_1-C_2 alkyl,

substituted (heterocycloalkyl)C_1-C_2 alkyl chosen from mono-, di-, and tri-substituted (heterocycloalkyl)C_1-C_2 alkyl, wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

pyridyl,

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

pyrimidinyl, and

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyrimidinyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6

alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl.

[0074] When referring to compounds of Formula I, in some embodiments, R_2 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are indepedently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are indepedently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl.

[0075] When referring to compounds of Formula I, in some embodiments, R_2 is chosen from

phenyl substituted with at least one branched C_3-C_6alkyl, and further substituted with 0 to 2 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl, and

pyridyl substituted with at least one branched C_3-C_6alkyl, and further substituted with 0 to 2 substituents independently chosen from

hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl.

[0076] When referring to compounds of Formula I, in some embodiments, R_2-Q- is chosen from

halo-C_1-C_4 alkyl,

phenoxy and

substituted phenoxy chosen from mono-, di-, and tri-substituted phenoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

[0077] In some embodiments,

R_2-Q- is chosen from

chloro-C_1-C_4 alkyl,

phenoxy, and

substituted phenoxy chosen from mono-, di-, and tri-substituted phenoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4alkyl).

[0078] In some embodiments, R_2-Q- is halo-C_1-C_4 alkyl. In some embodiments, R_2-Q- is chosen from

phenoxy and

substituted phenoxy chosen from mono-, di-, and tri-substituted phenoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

[0079] When referring to compounds of Formula I, in some embodiments,

R_6 is chosen from hydrogen, C_1-C_6 alkyl, and phenyl;

R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl,

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyrimidinyl, and

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyrimidinyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

phenylene,

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

naphthylidene, and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

R_2-Q- is chosen from

chloro-C_1-C_4 alkyl,

phenoxy, and

substituted phenoxy chosen from mono-, di-, and tri-substituted phenoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4alkyl).

[0080] When referring to compounds of Formula I, in some embodiments,

R_6 is chosen from hydrogen, C_1-C_6 alkyl, and phenyl;

R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl,

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6

alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyrimidinyl, and

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyrimidinyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

phenylene,

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

pyridylidene,

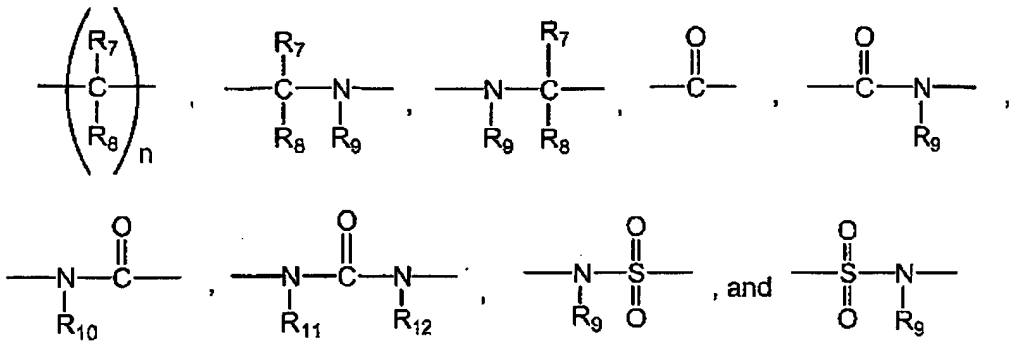
substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

naphthylidene, and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2

haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo, and n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from hydrogen, C_1-C_6 alkyl, and phenyl;

R_2 is chosen from

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

(C_3-C_7 cycloalkyl)methyl,

substituted (C_3-C_7 cycloalkyl)methyl chosen from mono-, di-, and tri-substituted (C_3-C_7 cycloalkyl)methyl wherein the substituents are independently chosen from

hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

(heterocycloalkyl)C_1-C_2 alkyl,

substituted (heterocycloalkyl)C_1-C_2 alkyl chosen from mono-, di-, and tri-substituted (heterocycloalkyl)C_1-C_2 alkyl, wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

pyridyl,

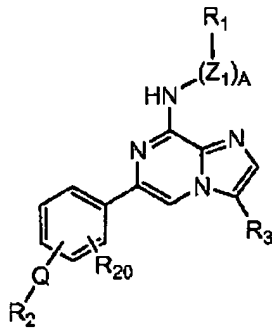
substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-

C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

pyrimidinyl, and

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyrimidinyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl.

[0081] In another embodiment, the invention provides at least one chemical entity chosen from compounds of Formula 2:



(Formula 2)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1, Q, R_2, R_3, Z_1, and A are as described for compounds of Formula I, and further wherein

R_{20} represents 0, 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl). In some

embodiments, R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

[0082] When referring to compounds of Formula 2, in some embodiments, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

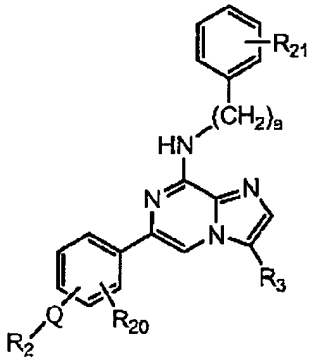
substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6

alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

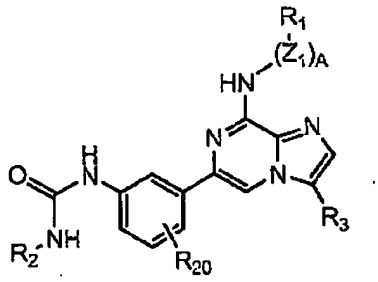
[0083] Some embodiments provide at least one chemical entity chosen from compounds of Formula 3



(Formula 3)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein Q, R_2 and R_3 are as described for compounds of Formula 1; a is chosen from 0, 1, 2 and 3; R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl); and R_{21} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6alkoxycarbonyl. In some embodiments, R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents 1 substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

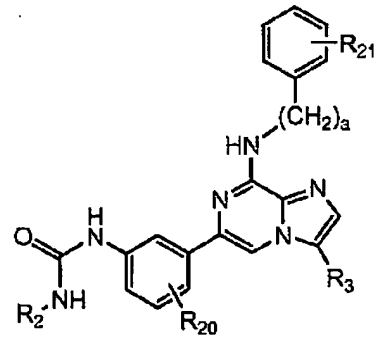
[0084] Some embodiments provide at least one chemical entity chosen from compounds of Formula 4



(Formula 4)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_2, R_3, Z_1, and A are as described for compounds of Formula 1, and further wherein R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl).

[0085] Some embodiments provide at least one chemical entity chosen from compounds of Formula 5



(Formula 5)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_3 is as described for compounds of Formula 1, and further wherein

a is chosen from 0, 1, 2 and 3;

R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl);

R_{21} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6alkoxycarbonyl; and

R_2 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are indepedently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl,

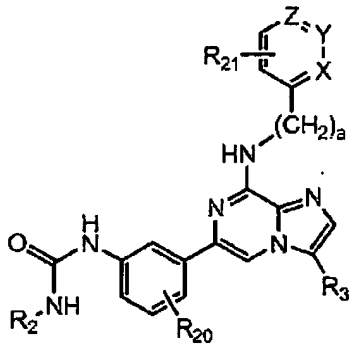
pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are indepedently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl.

In some embodiments, R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-

C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents 1 substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl).

[0086] Some embodiments provide at least one chemical entity chosen from compounds of Formula 6



(Formula 6)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_3 is as described for compounds of Formula 1, and R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl alkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6

alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

substituted (C_3-C_7 cycloalkyl)methyl chosen from mono-, di-, and tri-substituted (C_3-C_7 cycloalkyl)methyl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

substituted (heterocycloalkyl)C_1-C_2 alkyl, chosen from mono-, di-, and tri-substituted (heterocycloalkyl)C_1-C_2 alkyl, wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl;

a is chosen from 0, 1, 2 and 3;

X, Y, and Z are chosen from nitrogen and CH, wherein one and only one of X, Y, and Z is nitrogen; and

R_{21} represents 0 to 4 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

In some embodiments, R_2 is chosen from

phenyl,

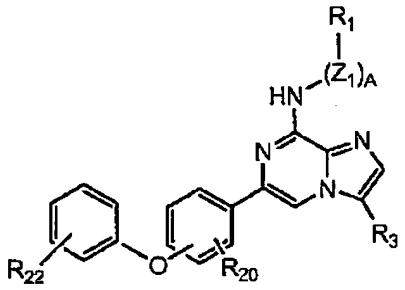
substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl.

[0087] Some embodiments provide at least one chemical entity chosen from

compounds of Formula 7



(Formula 7)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof wherein Z_1, R_3, and A are as described for Formula 1, and further wherein R_1 is chosen from

C_3-C_7 cycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano,

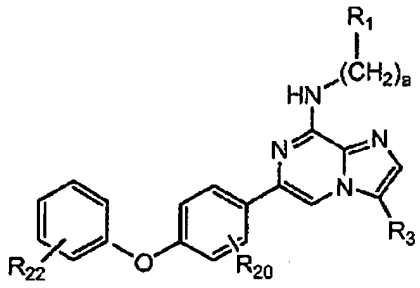
carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl); and

R_{22} represents 0 to 4 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

In some embodiments, R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents 1 substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl).

[0088] Some embodiments provide at least one chemical entity chosen from compounds of Formula 8

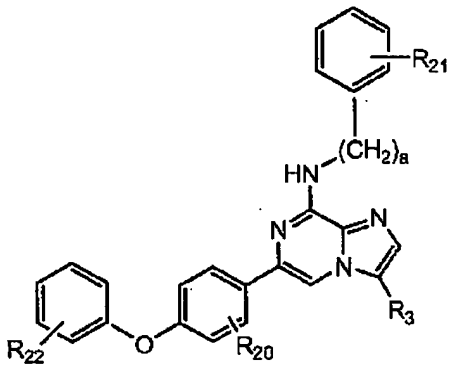


(Formula 8)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_3, R_{20}, and R_{22} are as described for compounds of Formula 7; and further wherein a is chosen from 0 and 1.

[0089] Some embodiments provide at least one chemical entity chosen from

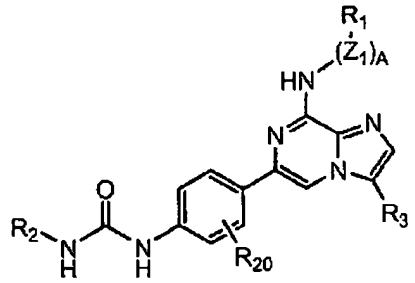
compounds of Formula 9



(Formula 9)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_3, R_{20}, R_{22}, and a are as described for compounds of Formula 8; and further wherein R_{21} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

[0090] Some embodiments provide at least one chemical entity chosen from compounds of Formula 10



(Formula 10)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_3, Z_1, and A are as described for Formula 1; and R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl alkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

substituted (C_3-C_7 cycloalkyl)methyl chosen from mono-, di-, and tri-substituted (C_3-C_7 cycloalkyl)methyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy,

C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

substituted (heterocycloalkyl)C_1-C_2 alkyl chosen from mono-, di-, and tri-substituted (heterocycloalkyl)C_1-C_2 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

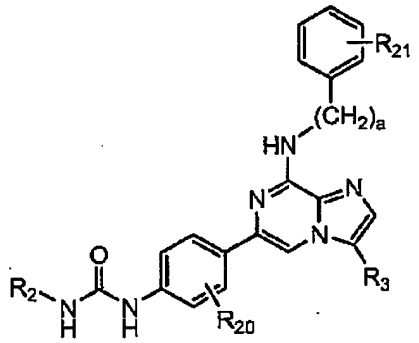
substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano,

amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

In some embodiments, R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents 1 substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl).

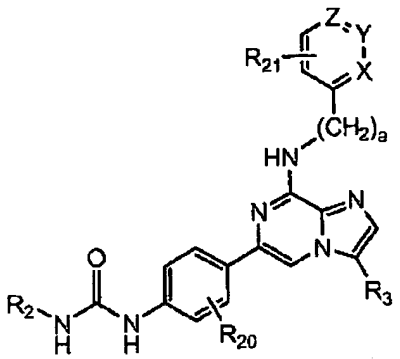
[0091] Some embodiments provide at least one chemical entity chosen from compounds of Formula 11



(Formula 11)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_2, R_3, and R_{20} are as described for Formula 10, and further wherein a is chosen from 0, 1, 2, and 3; and R_{21} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

[0092] Some embodiments provide at least one chemical entity chosen from compounds of Formula 12



(Formula 12)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_3, and R_{20} are as described for Formula 10; and further wherein

a is chosen from 0, 1, 2, and 3;

X, Y, and Z are chosen from nitrogen and CH, wherein one and only one of X, Y, and Z is nitrogen;

R_2 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl,

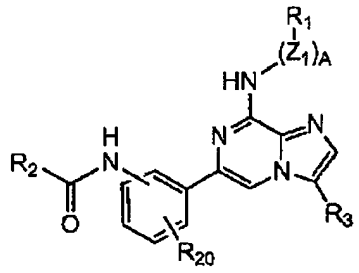
pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6alkylthio,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl; and

R_{21} represents 0 to 4 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6alkoxycarbonyl.

[0093] Some embodiments provide at least one chemical entity chosen from compounds of Formula 13



(Formula 13)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_3, Z_1, and A are as described in Formula 1; and further wherein R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

substituted (C_3-C_7 cycloalkyl)methyl chosen from mono-, di-, and tri-substituted (C_3-C_7 cycloalkyl)methyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

substituted (heterocycloalkyl)C_1-C_2 alkyl chosen from mono-, di-, and tri-substituted (heterocycloalkyl)C_1-C_2 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6

alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-

C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and s

ubstituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

[0094] When referring to compounds of Formula 13, in some embodiments, R_2 is chosen from

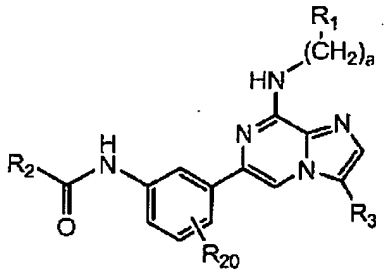
phenyl substituted with at least one branched C_3-C_6alkyl, and further substituted with 0 to 2 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl, and

pyridyl substituted with at least one branched C_3-C_6alkyl, and further substituted with 0 to 2 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl.

[0095] In some embodiments, R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents 1 substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl).

[0096] Some embodiments provide at least one chemical entity chosen from compounds of Formula 14



(Formula 14)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_2, R_3, and R_{20} are as described in Formula 13; and further wherein a is chosen from 0 and 1.

[0097] When referring to compounds of Formula 14, in some embodiments, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6 alkoxycarbonyl,

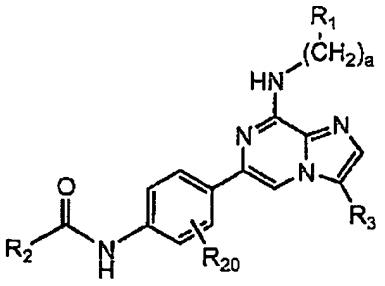
benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6 alkoxycarbonyl.

[0098] Some embodiments provide at least one chemical entity chosen from compounds of Formula 15



(Formula 15)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_2, R_3, and R_{20} are as described in Formula 13; and further wherein a is chosen from 0 and 1. When referring to compounds of Formula 15, in some embodiments, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

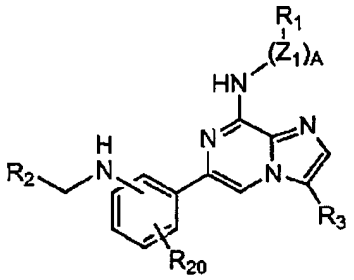
benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

[0099] Some embodiments provide at least one chemical entity chosen from compounds of Formula 16



(Formula 16)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_3, Z_1, and A are as described in Formula 1; and further wherein R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

substituted (C_3-C_7 cycloalkyl)methyl chosen from mono-, di-, and tri-substituted (C_3-C_7 cycloalkyl)methyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

substituted (heterocycloalkyl)C_1-C_2 alkyl chosen from mono-, di-, and tri-substituted (heterocycloalkyl)C_1-C_2 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from

hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-

C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

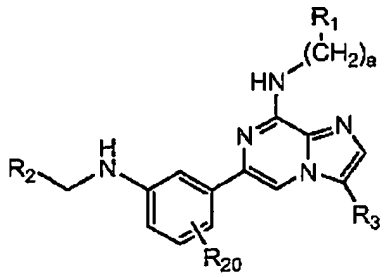
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4alkyl).

In some embodiments, R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents 1 substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl).

[00100] Some embodiments provide at least one chemical entity chosen from compounds of Formula 17



(Formula 17)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_2, R_3, and R_{20} are as described in Formula 16; and further wherein a is chosen from 0 and 1. When referring to compounds of Formula 17, in some embodiments, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

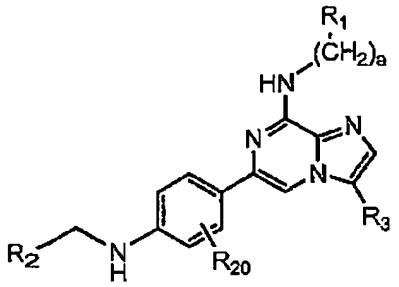
benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 baloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

[00101] Some embodiments provide at least one chemical entity chosen from compounds of Formula 18



(Formula 18)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_2, R_3, and R_{20}, are as described in Formula 16; and further wherein a is chosen from 0 and 1. In some embodiments, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

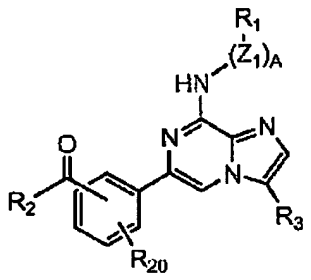
substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6

alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

[00102] Some embodiments provide at least one chemical entity chosen from compounds of Formula 19



(Formula 19)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_3, Z_1, and A are as described in Formula 1; and further wherein R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

substituted (C_3-C_7 cycloalkyl)methyl chosen from mono-, di-, and tri-substituted (C_3-C_7 cycloalkyl)methyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

substituted (heterocycloalkyl)C_1-C_2 alkyl chosen from mono-, di-, and tri-substituted (heterocycloalkyl)C_1-C_2 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted (C_1-C_6 alkoxy)C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano,

amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

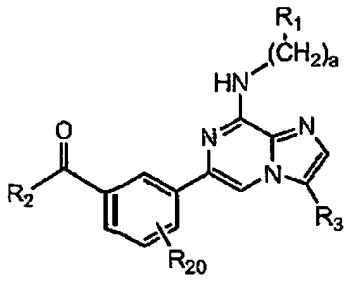
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

In some embodiments, R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl). In some embodiments, R_{20} represents 1 substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl).

[00103] Some embodiments provide at least one chemical entity chosen from compounds of Formula 20



(Formula 20)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_2, R_3, and R_{20}, are as described in Formula 19, and further wherein a is chosen from 0 and 1. When referring to compounds of Formula 20, in some embodiments, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

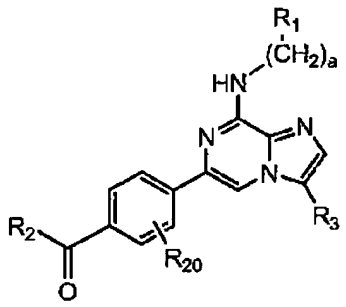
substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl,

C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6alkox

[00104] Some embodiments provide at least one chemical entity chosen from compounds of Formula 21



(Formula 21)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein R_1, R_2, R_3, and R_{20}, are as described in Formula 19, and further wherein a is chosen from 0 and 1. When referring to compounds of Formula 21, in some embodiments, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-

(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

[00105] In some embodiments, at least one chemical entity is chosen from

1-(4-Chloro-phenyl)-3-[3-(8-methylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea,

1-(4-Chloro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea,

1-(4-Chloro-phenyl)-3-{3-[8-(4-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea,

1-(4-Chloro-phenyl)-3-{3-[8-(3-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea,

1-(4-Chloro-phenyl)-3-{3-[8-(2-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea,

1-(4-Chloro-phenyl)-3-{3-[8-(pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea,

1-{3-[8-(4-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea,

1-{3-[8-(3-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea,

1-{4-[8-(4-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea,

1-{4-[8-(3-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea,

4-(6-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester,

Cyclopropylmethyl-[6-(4-phenoxy-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine,

(2-Methoxy-benzyl)-[6-(4-phenoxy-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine,

Benzo[1,3]dioxol-5-ylmethyl-[6-(4-phenoxy-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine,

[6-(4-Chloromethyl-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-(2-methoxy-benzyl)-amine,

1-{4-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-phenyl-urea,

(2-Methoxy-benzyl)-{6-[4-(4-methoxy-benzylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-yl}-amine,

(2-Methoxy-benzyl)-{6-[3-(4-methoxy-benzylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-yl}-amine,

1-{3-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-phenyl-urea,

1-(2-Chloro-phenyl)-3-{4-[8-(2-methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea,

1-{4-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(2-methoxy-phenyl)-urea,

1-{4-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-methoxy-phenyl)-urea,

4-{6-[4-(Piperidine-1-carbonyl)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester,

4-(6-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester,

4-(6-{3-[3-(2-Methylsulfanyl-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester,

{4-[8-(4-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-

piperidin-1-yl-methanone,

{4-[8-(2-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-piperidin-1-yl-methanone,

3-Methoxy-N-{4-[8-(2-methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide,

1-(3-Chloro-4-fluoro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea,

1-(4-Chloro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea,

1-[3-(8-Phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea,

1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea,

1-(4-Chloro-phenyl)-3-{3-[8-(4-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea,

1-{3-[8-(4-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-trifluoromethyl-phenyl)-urea,

1-(3-Chloro-4-fluoro-phenyl)-3-{3-[8-(3-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea,

1-(4-Chloro-phenyl)-3-{3-[8-(3-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea,

1-{3-[8-(3-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-trifluoromethyl-phenyl)-urea,

1-(3-Chloro-4-fluoro-phenyl)-3-{3-[8-(2-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, and

1-(3-Chloro-4-fluoro-phenyl)-3-{3-[8-(2-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea,

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof.

[00106] In some embodiments, at least one chemical entity is chosen from

4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-

8-ylamino}-benzoic acid,

4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid,

4-{6-[5-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid,

4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester, and

4-tert-Butyl-N-{2-methyl-5-[8-(4-sulfamoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide,

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof.

[00107] Methods for obtaining the compounds described herein are known to those of ordinary skill in the art, suitable procedures being described, for example, in the references cited herein. See, also, U.S. patent application No. 10/861,791; PCT/US04/18227; U.S. patent application No. 10/915,696; and PCT/US04/025884, each of which is incorporated by reference herein for all purposes.

[00108] As mentioned above, it is believed that the interaction of the chemical entities described herein with one or more kinases results in modulation of the activity of the one or more kinases. Suitable kinases include but are not limited to tyrosine kinases and serine/threonine kinases, which may be classified as including the AGC group (cyclic nucleotide regulated family) of protein kinases, which includes the cyclic nucleotide regulated protein kinase family (e.g., PKA and PKG), the diacylglycerol-activated/phospholipid-dependent family protein kinase C family (e.g., PKC), the PKA and PKC-related family (e.g., RAC and Akt), the kinases that phosphorylate G protein-coupled receptors family, the budding yeast AGC-related protein kinase family, the kinases that phosphorylate ribosomal protein S6 family, the budding yeast DBF2/20 family, the flowering plant PVPK1 protein kinase homolog family, and other AGC related kinase families.

[00109] The CaMK (calcium calmodulin dependent) group of protein kinases includes kinases regulated by Ca^{2+}/CaM and close relatives family, the KIN1/SNF1/Nim1 family, and other related CaMK related kinase families. The

CMGC group (named because it includes the cyclin-dependent kinases) includes the cyclin-dependent kinases (e.g., CDKs) and close relatives family, the ERK (e.g., MAP) kinase family, the glycogen synthase 3 (e.g., GSK3) family, the casein kinase II family, the Clk family and other CMGC kinases.

[00110] The PTK group of protein kinases includes protein-tyrosine kinases that may be nonmembrane-spanning or membrane-spanning tyrosine kinases. The PTK group of protein kinases includes the Src family, the Tek/Atk family, the Csk family, the Fes (Fps) family, the Abl family, the Syk/ZAP70 family, the Ttk2/Jak1 family, the Ack family, the focal adhesion kinase (Fak) family, the epidermal growth factor receptor family, the Eph/Elk/Eck receptor family, the Axl family, the Tie/Tek family, the platelet-derived growth factor receptor family, the fibroblast growth factor receptor family, the insulin receptor family, the LTK/ALK family, the Ros/Sevenless family, the Trk/Ror family, the DDR/TKT family, the hepatocyte growth factor receptor family, the nematode Kin15/16 family and other PTK kinase families.

[00111] The OPK group (other protein kinases) includes the Polo family, the MEK/STE7 family, the PAK/STE20 family, the MEKK/STE11 family, the NimA family, the wee1/mik1 family, the kinases involved in transcriptional control family, the Raf family, the Activin/TGFb receptor family, the flowering plant putative receptor kinases and close relatives family, the PSK/PTK leucine zipper domain family, the casein kinase I family, the PKN prokaryotic protein kinase family and other OPK protein kinase families. A large number of kinases are found in G. Hardie *et al., Protein Kinase Facts Book* 0-12-324719-5 (1995).

[00112] Accordingly, a method of treating a kinase-implicated disease or condition in a mammal, such as a human, comprises administration to the mammal of a pharmaceutical composition comprising a therapeutically effective amount of at least one chemical entity chosen from compounds of Formula I and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, and a pharmaceutically acceptable carrier. As used herein "therapeutically effective" includes alleviation of disease, disease symptoms, preventative, and prophylactic treatment.

[00113] Kinases are implicated in a large variety of diseases, as certain

mutations in protein kinases can lead to activation of pathways causing, for example, the production of tumors, while other mutations in protein kinases block pathways and prevent a response. Some diseases that are linked to mutations in protein kinases are listed in the KinMutBase database (http://www.uta.fi/imt/bioinfo/KinMutBase/) (Stenberg et al., Nucleic Acids Research, Vol. 28, pp. 369-372, 2000). Diseases caused by protein kinase mutations include X-linked agammaglobulinemia (XLA), and non-insulin dependent diabetes mellitus (NIDDM), and severe combined immunodeficiency (SCID). Mutations related to tumor development have been liked to such diseases as Hirschprung's disease, multiple endocrine neoplasia type 2 (MEN2) a and b, medullary thyroid carcinoma (FMTC), papillary renal carcinoma (HPRC), and Peutz-Jeghers syndrome.

[00114] Mutations in growth factor receptor kinases are linked to diseases such as mastocytosis, systemic mast cell disease, piebaldism, hypochondroplasia, thanatophoric dysplasia, and skeletal dysplasia. Other protein kinase-linked diseases include Coffin-Lowry syndrome, congenital insensitivity to pain with anhidrosis (CIPA), hypertension, vascular dysplasia, errors in vascular morphogenesis, and X-linked mental retardation. Mutations in protein kinases have also been linked to neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD).

[00115] Other diseases associated with protein kinases include Gaucher disease, hypochromic anemia, granulomatous disease, ataxia-telangiectasia, familial hypercholesterolemia, certain types of muscular dystrophy such as Driefuss-Emory type, cystic fibrosis, type 1 hyperlipoproteinemia, Treacher Collins Franceschetti syndrome 1, Tay-Sachs disease, type 1 neurofibromatosis, adenomatous polyposis of the colon, X-linked ichthyosis, and Beckwith-Weidemann Syndrome.

[00116] Altered PKA (cyclic AMP-dependent protein kinase) expression is implicated in a variety of disorders and diseases including cancer, thyroid disorders, diabetes, atherosclerosis, and cardiovascular disease. Altered MAP (mitogen-activated protein) kinase expression is implicated in a variety of disease conditions including cancer, inflammation, immune disorders, and disorders affecting growth and development. RTKs (receptor tyrosine kinases), CDKs and STKs

(serine/threonine kinases) have all been implicated in a host of pathogenic conditions including, significantly, large number of diverse cancers. Others pathogenic conditions that have been associated with PTKs include, psoriasis, hepatic cirrhosis, diabetes, atherosclerosis, angiogenesis, restinosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, autoimmune disease, and a variety of renal disorders.

[00117] The conditions, diseases and/or disorders that can be affected using at least one chemical entity described herein and compositions comprising such chemical entities include, but are not limited to, psoriasis, cancer (for example, chronic myelogenous leukemia, gastrointestinal stromal tumors, non-small cell lung cancer, breast cancer, ovarian cancer, recurrent ovarian cancer, prostate cancer such as hormonal refractory prostate cancer, kidney cancer, head and neck cancer, or colorectal cancer), immunoregulation (graft rejection), atherosclerosis, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, diabetes (for example insulin resistance or diabetic retinopathy), septic shock, and the like.

[00118] In some embodiments, the condition is cancer. A method of treating cancer comprising administering to a mammal in need thereof a therapeutically effective amount of at least one chemical entity chosen from compounds of Formula I and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, and a therapeutically effective amount of an antitumor therapeutic. Treatment with the antitumor therapeutic may be prior to treatment with at least one chemical entity described herein, during treatment, following treatment with the at least one chemical entity, or a combination thereof. Suitable antitumor therapeutics are known, and include a chemotherapeutic agent, for example, chosen from mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, and doxorubicin. Radiotherapeutic antitumor agents may also be used, alone or in combination with chemotherapeutic agents.

[00119] In another embodiment, pharmaceutical compositions comprising at least one chemical entity chosen from compounds of Formula I and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, together with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents

and/or adjuvants, and if desired other active ingredients. Such pharmaceutical compositions include packaged pharmaceutical compositions for treating disorders responsive to modulation of kinase activity. A packaged pharmaceutical composition includes a container holding a therapeutically effective amount of at least one chemical entity chosen from compounds of Formula I and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, and instructions (e.g., labeling) indicating that the contained composition is to be used for treating a disorder responsive to kinase modulation in the patient. Those of ordinary skill in the art will also recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, mineral oil, vegetable oil, and dimethylsulfoxide (DMSO).

[00120] The chemical entities described herein may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles. In some embodiments, the compounds are administered orally in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques. The pharmaceutical compositions containing at least one chemical entity chosen from compounds of Formula I and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[00121] Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be

for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[00122] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[00123] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, which may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[00124] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil, or coconut

oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin, or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[00125] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring, and coloring agents, may also be present.

[00126] Suitable pharmaceutical compositions for therapeutic use may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

[00127] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a

solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00128] The chemical entities described herein may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[00129] The chemical entities described herein may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives, and buffering agents can be dissolved in the vehicle.

[00130] For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It is convenient to formulate these animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its diet. It is also convenient to present the composition as a premix for addition to the feed or drinking water.

[00131] Dosage levels of the order of from about 0.1 milligram to about 140 milligram per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 milligram to about 7 gram per human patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 milligram of an active ingredient.

[00132] Frequency of dosage may also vary depending on the chemical entity used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is used. For the treatment of eating disorders, including obesity, a dosage regimen of 1 or 2 times daily is used. For the treatment of impotence a single dose that rapidly reaches effective concentrations is used. It will

be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific chemical entity employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[00133] Chemical entities described herein will have at least one pharmacological property. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding, and desirable *in vitro* and *in vivo* half-lives.

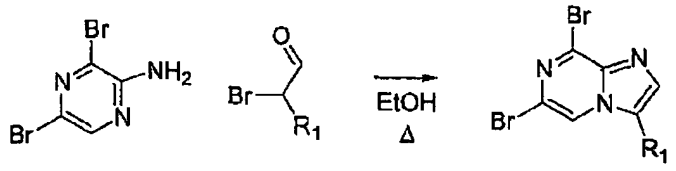
[00134] Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

[00135] Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (*Journal of Chromatography B* 1996, volume 677, pages 1-27).

[00136] In general, compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (*Drug Metabolism and Disposition* 1998, volume 26, pages 1120-1127).

[00137] In another embodiment, the chemical entities are used as probes for the localization of kinases of therapeutic interest, that is, for both in vivo and in vitro identification and isolation the specific proteins to which it binds. A method for identifying a kinase comprises contacting an organism, cell, or preparation comprising the kinase with at least one chemical entity chosen from compounds of Formula I and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, and detecting modulation of an activity of the kinase. Suitable methods for detecting kinase modulation are known, for example those described herein.

[00138] The invention is further illustrated by the following non-limiting examples.

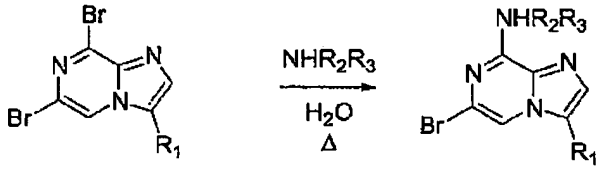


1 2 3

Example 1. Synthesis of compounds of Formula 1 (FIGURE 1).

[00139] 6,8-dibromoimidazo[1,2-a]pyrazine (3). A solution of 1.00 equivalents (eq.) of 3,5-dibromo-2-aminopyrazine 1 in ethanol is treated with 2.00 eq. of α-bromo-aldehyde 2 at room temperature (RT) and heated for 48 hours (hr). The solvent is removed under reduced pressure and the residue is triturated with diethyl ether and filtered to give the HBr salt 3.

[00140] 8-Amino-6-bromoimidazo[1,2-a]pyrazine (4). Procedure 1: A mixture

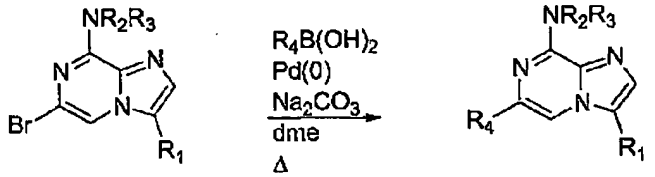


3 4

of 1.00 eq. of 6,8-imidazo[1,2-a]pyrazine 3 in 28 % ammonia/water solution or 40% aqueous methyl amine is heated to between 80 to 90°C for 24 hr. The resulting mixture is partitioned between CH_2Cl_2 and H_2O. The aqueous layer is extracted with CH_2Cl_2 and the combined organic extracts are dried over Na_2SO_4. The solvent is removed under reduced pressure and the resulting residue is crystallized from ethanol to yield 4.

[00141] Procedure 2: A solution of 1.00 eq. of 6,8-imidazo[1,2-a]pyrazine 3 in N,N-dimethylacetamide is treated with 2.00 eq. of benzylamine and 3.00 eq. of K_2CO_3. The resulting mixture is heated to 100°C for 24 to 48 hours, cooled to RT and partitioned between H_2O/CH_2Cl_2. The aqueous layer is extracted with CH_2Cl_2 and combined organic extracts are dried over Na_2SO_4. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (3:7

ethyl acetate (EtOAc)/Hexanes) to yield 4.



4 5

[00142] 8-Amino-6-aryl-imidazo[1,2-a]pyrazine (5). A mixture of 1.00 eq. of 8-amino-6-bromoimidazo[1,2-a]pyrazine, 3.00 eq. of R_4-substituted boronic acid, and 0.10 eq. of Pd $(PPh_{3b})_4$, in 6.00 eq. of 1N Na_2CO_3/dme is heated to 90°C for 24 hr. The mixture is cooled to RT and partitioned between 10% acetic acid (AcOH)/CH_2Cl_2. The aqueous phase is extracted with CH_2Cl_2 and combined extracts are dried over Na_2SO_4. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (1-5% 2M NH_3/methanol/CH_2Cl_2) to yield 5.

Example 2. Synthesis of compounds of Formula 1b (FIGURE 2).

[00143] 8-Amino-6-aryl-imidazo[1,2-a]pyrazine (6). A mixture of 1.00 eq. of 8-amino-6-bromoimidazo[1,2-a]pyrazine, 3.00 eq. of R_4-sustituted boronic acid, and 0.10 eq. of Pd $(PPh_3)_4$, in 4.00 eq. of 1N Na_2CO_3/dme is heated to 90°C for 24 hr. The mixture is cooled to RT and partitioned between EtOAc/saturated $NaHCO_3$. The aqueous phase is extracted with EtOAc and the combined extracts are dried over Na_2SO_4. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (1-5% 2M NH_3/methanol/EtOAc) to yield 6.

[00144] N-[3-(8-Benzylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide (8). A solution of 1.00 eq. of 8-amino-6-aryl-imidazo[1,2-a]pyrazine in toluene/DMA is treated dropwise with 1.00 eq. of aryl acid chloride and stirred at RT for 10 hr. The resulting mixture is partitioned between EtOAc/saturated $NaHCO_3$. The aqueous phase is extracted with EtOAc and the combined extracts are dried over Na_2SO_4. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (1-5% methanol/EtOAc) to yield 8.

[00145] N-[3-(8-Benzylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-

benzenesulfonamide (9). A solution of 1.00 eq. of 8-amino-6-aryl-imidazo[1,2-a]pyrazine in 5% N-methyl morpholine (NMM)/toluene is treated dropwise with 1.1 eq of aryl sulfonyl chloride and heated to 50°C for 8 h. The solution is cooled to RT and partitioned between EtOAc/saturated $NaHCO_3$. The aqueous phase is extracted with EtOAc and the combined extracts are dried over Na_2SO_4. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography ((1-5% methanol/EtOAc) to yield 9.

[00146] 1-[3-(8-Benzylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-3-phenyl-urea (10). A solution of 1.00 eq. of 8-amino-6-aryl-imidazo[1,2-a]pyrazine in 5% NMM/toluene is treated dropwise with 1.0 eq of aryl isocyanate and heated to 60°C for 8 hr. The solution is cooled to RT and partitioned between EtOAc/saturated $NaHCO_3$. The aqueous phase is extracted with EtOAc and the combined extracts are dried over Na_2SO_4. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (1-5% 2M NH_3/MeOH/EtOAc) to yield 10.

Example 3. The following compounds were prepared in accordance with FIGURES 1 and 2 using the above procedures.

(a) 1-(4-Chloro-phenyl)-3-[3-(8-methylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF=$C_{20}H_{17}ClN_6O$, MW=392.84 Mass Spec m/z (M^+ +1) 393.06.

(b) 1-(4-Chloro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF = $C_{25}H_{19}ClN_6O$ MW=454.91 Mass Spec m/z (M^+ +1) 455.04.

(c) 1-(4-Chloro-phenyl)-3-{3-[8-(4-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=$C_{25}H_{18}Cl_2N_6O$, MW=489.36 Mass Spec m/z (M^+ +1) 489.20.

(d) 1-(4-Chloro-phenyl)-3-{3-[8-(3-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=$C_{25}H_{18}Cl_2N_6O$, MW=489.36 Mass Spec m/z (M^+ +1) 489.13.

(e) 1-(4-Chloro-phenyl)-3-{3-[8-(2-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=$C_{25}H_{18}Cl_2N_6O$, MW=489.36 Mass Spec m/z (M^+ +1) 489.04.

(f) 1-(4-Chloro-phenyl)-3-{3-[8-(pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=$C_{24}H_{18}ClN_7O$, MW=455.90 Mass Spec m/z (M^+ +1) 456.07.

(g) 1-{3-[8-(4-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea, MF=$C_{26}H_{20}Cl_2N_6O$, MW=503.38 Mass Spec m/z (M^+ +1) 503.04.

(h) 1-{3-[8-(3-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea, MF=$C_{26}H_{20}Cl_2N_6O$, MW=503.38 Mass Spec m/z (M^+ +1) 503.01.

(i) 1-{4-[8-(4-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea, MF=$C_{26}H_{20}Cl_2N_6O$, MW=503.38 Mass Spec m/z (M^+ +1) 503.01.

(j) 1-{4-[8-(3-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea, MF=$C_{26}H_{20}Cl_2N_6O$, MW=503.38 Mass Spec m/z (M^+ +1) 503.01.

(k) 4-(6-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester, MF= $C_{28}H_{23}ClN_6O_3$, MW= 526.97 Mass Spec m/z (M^+ +1) 527.05.

(l) Cyclopropylmethyl-[6-(4-phenoxy-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine, MF=$C_{22}H_{20}N_4O$, MW=356.42 Mass Spec m/z (M^+ +1) 357.19.

(m) (2-Methoxy-benzyl)-[6-(4-phenoxy-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine, MF= $C_{26}H_{22}N_4O_2$, MW= 422.48 Mass Spec m/z (M^+ +1) 423.19.

(n) Benzo[1,3]dioxol-5-ylmethyl-[6-(4-phenoxy-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine, MF= $C_{26}H_{20}N_4O_3$, MW= 436.46 Mass Spec m/z (M^+ +1) 437.18.

(o) [6-(4-Chloromethyl-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-(2-methoxy-benzyl)-amine, MF= $C_{21}H_{19}ClN_4O$, MW= 378.85 Mass Spec m/z (M^+ +1) 379.13.

(p) 1-{4-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-phenyl-urea, MF= $C_{27}H_{24}N_6O_2$, MW= 464.52 Mass Spec m/z (M^+ +1) 465.07.

(q) (2-Methoxy-benzyl)-{6-[4-(4-methoxy-benzylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-yl}-amine, MF= $C_{28}H_{27}N_5O_2$, MW= 465.55 Mass Spec m/z (M^+ +1) 466.10.

(r) (2-Methoxy-benzyl)-{6-[3-(4-methoxy-benzylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-yl}-amine, MF= $C_{28}H_{27}N_5O_2$, MW= 465.55 Mass Spec m/z (M^+ +1) 466.09.

(s) 1-{3-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-phenyl-urea, MF= $C_{27}H_{24}N_6O_2$, MW= 464.52 Mass Spec m/z (M^+ +1) 465.05.

(t) 1-(2-Chloro-phenyl)-3-{4-[8-(2-methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=$C_{27}H_{23}ClN_6O_2$, MW=498.96 Mass Spec m/z (M^+ +1) 499.18.

(u) 1-{4-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(2-methoxy-phenyl)-urea, MF= $C_{28}H_{26}N_6O_3$, MW= 494.54 Mass Spec m/z (M^+ +1) 495.22.

(v) 1-{4-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-methoxy-phenyl)-urea, MF= $C_{28}H_{26}N_6O_3$, MW= 494.54 Mass Spec m/z (M^+ +1) 495.21.

(w) 4-{6-[4-(Piperidine-1-carbonyl)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester, MF=$C_{27}H_{27}N_5O_3$, MW=469.54 Mass Spec m/z (M^+ +1) 470.08.

(x) 4-(6-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester, MF=$C_{28}H_{23}ClN_6O_3$, MW=526.97 Mass Spec m/z (M^+ +1) 527.05.

(y) 4-(6-{3-[3-(2-Methylsulfanyl-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester, MF=$C_{29}H_{26}N_6O_3S$, MW=538.62 Mass Spec m/z (M^+ +1) 539.18.

(z) {4-[8-(4-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-piperidin-1-yl-methanone, MF=$C_{24}H_{22}ClN_5O$, MW=431.92 Mass Spec m/z (M^+ +1) 432.03.

(aa) {4-[8-(2-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-piperidin-1-yl-methanone, MF=$C_{24}H_{22}ClN_5O$, MW=431.92 Mass Spec m/z

(M^+ +1) 432.03.

(bb) 3-Methoxy-N-{4-[8-(2-methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide, MF=$C_{28}H_{25}N_5O_3$, MW=479.53 Mass Spec m/z (M^+ +1) 479.99.

(cc) 1-(3-Chloro-4-fluoro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF=$C_{25}H_{18}ClFN_6O$, MW= 472.90 Mass Spec m/z (M^+ +1) 473.01.

(dd) 1-(4-Chloro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF=$C_{25}H_{19}ClN_6O$, MW=454.91 Mass Spec m/z (M^+ +1) 455.04.

(ee) 1-[3-(8-Phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea, MF=$C_{26}H_{19}F_3N_6O$, MW=488.46 Mass Spcc m/z (M^+ +1) 489.01.

(ff) 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF=$C_{26}H_{18}ClF_3N_6O$, MW=522.91 Mass Spec m/z (M^+ +1) 523.11.

(gg) 1-(4-Chloro-phenyl)-3-{3-[8-(4-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=$C_{25}H_{18}Cl_2N_6O$, MW=489.36 Mass Spec m/z (M^+ +1) 489.20.

(hh) 1-{3-[8-(4-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-trifluoromethyl-phenyl)-urea, MF=$C_{26}H_{18}ClF_3N_6O$, MW=522.91 Mass Spec m/z (M^+ +1) 523.13.

(ii) 1-(3-Chloro-4-fluoro-phenyl)-3-{3-[8-(3-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=$C_{25}H_{17}Cl_2FN_6O$, MW=507.35 Mass Spec m/z (M^+ +1) 507.13.

(jj) 1-(4-Chloro-phenyl)-3-{3-[8-(3-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=$C_{25}H_{18}Cl_2N_6O$, MW=489.36 Mass Spec m/z (M^+ +1) 489.13.

(kk) 1-{3-[8-(3-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-trifluoromethyl-phenyl)-urea, MF=$C_{26}H_{18}ClF_3N_6O$, MW=522.91 Mass Spec m/z (M^+ +1) 523.12.

(ll) 1-(3-Chloro-4-fluoro-phenyl)-3-{3-[8-(2-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=$C_{25}H_{17}Cl_2FN_6O$, MW=507.35 Mass Spec m/z (M^+ +1) 507.09.

(mm) 4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid, MF=$C_{31}H_{29}N_5O_3$, MW=519.59

(nn) 4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid, MF=$C_{31}H_{29}N_5O_3$, MW=519.59

(oo) 4-{6-[5-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid, MF=$C_{31}H_{29}N_5O_3$, MW=519.59

(pp) 4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester, MF=$C_{33}H_{33}N_5O_3$, MW=547.65

(qq) 4-tert-Butyl-N-{2-methyl-5-[8-(4-sulfamoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide, MF=$C_{30}H_{30}N_6O_3S$, MW=554.66

Example 4. A generalized description of the standard AKT-1 Kinase Assay that may be used to evaluate chemical entities is as follows.

[00147] In a final reaction volume of 40 microliters (µl), active recombinant N-terminus his-tagged AKT-1/PKBα kinase expressed in Sf21 cells (UBI # 14-276; 50-100 nanogram; 19-38 nanomolar; about 4.5-9 mU) is incubated in 25 mM Tris pH 7.6; 5 mM Beta-glycerophosphate; 2 mM DTT; 100 µM sodium vanadate; 10 mM $MgCl_2$ in 96-well Pierce Reaci-Bind™ streptavidin-coated high binding capacity coated white plate (Pierce # 15502) coated with saturating amounts of biotinylated Crosstide peptide (UBI #12-385; biotin-KGSGSGRPRTSSFAEG (SEQ ID NO:1); 50 picomoles; about 1.25 µM) and initiated with the addition of 2.5 µCi ^{32}P-γATP (specific activity 3000 Ci/mmole; 10 mCi/ml; about 21 nM). Compounds are tested initially in duplicate wells for determination of initial IC_{50} inhibition in half log serial dilutions starting at 100 µM with a final concentration of 2% DMSO. Following a 30 min incubation at 30°C, the reaction is stopped by aspiration and 4 x 100 µl washes with TBS plus 0.05% Tween-20 prior to addition of 100 µl scintillant and counting in Beckman TopCount instrument. Percent inhibition is calculated as [1-((AVE CPM

$_{compound}$ – AVE CPM $_{no\ peptide\ background}$)/(AVE CPM $_{no\ compound\ MAX}$ – AVE CPM $_{no\ peptide\ background}$)))*100]. Staurosporine, a general ATP competitive kinase inhibitor is used as a reference compound and shows an IC50 of approximately 60-100 nM for AKT-1 in the current assay format. Approximate S/N ratios are 8-12X with AVE CPM of Maximum about 15k and no peptide background about 1.5 K. Improved S/N ratios should be obtainable using higher amounts of either AKT-1 kinase or ^{32}P-γATP. Cold ATP is not added in current format but has been added at up to 200 μM in the presence of 5 μCi ^{32}P-γATP resulting in S/N ratios of approximately 5-10X.

Example 5. A generalized description of the standard assay to evaluate modulation of cell growth in soft agar (using cell lines HCT-15 (colon cancer), MiaPaca2 (pancreatic cancer), MCF-7 (breast cancer) and a NIH3T3 clone stably over-expressing transfected myrAkt-1 human gene, for example) is as follows.

[00148] Preparation of the agar base layer: A quantity of 500 ml of 2X DMEM (phenol red free, Sigma Cat # D2902) is prepared, and sterile filtered. To that solution is added 10 ml of sodium pyruvate (Gibco, Cat # 11360-070), 10 ml of penicillin/streptomycin (Gibco, Cat# 15140-122), 10 ml of Glutamax (Gibco, cat# 33050-061) and 100 ml of heat-inactivated FBS (Gemini) to make 2X DMEM complete media stock. Two stock concentrations of Sea Plaque low melt agar (Biowhittaker, Cat # 431097), 1%, and 0.6%, are prepared with ultra pure milliQ water, and sterilized by autoclaving. To prepare the agar base layer for a 12-well plate (Falcon # 353042), 6 ml of the 2X DMEM stock is mixed with 6 ml of 1% agar stock, both at 37°C, and 1 ml of the resulting mixture is added to each well of the 12 well plate, 3 hrs prior to setup of top layer.

[00149] Top layer with cells and compound for evaluation: Cells at 60-80% confluency (log growth) in T75 are trypsinized with 1 ml of 1x trypsin solution (Gibco), neutralized with 10 ml of 1x DMEM 10% FBS and viable cells counted using a hemocytometer via trypan blue exclusion. A working stock of 2.5 x 10^4 cells / ml is prepared in 1x DMEM 10% FBS. A 15 ml centrifuge tube is prepared for each concentration of compound tested in duplicate wells of a 12 well plate. The following are added in order: 1 ml of 2X DMEM stock at 37°C; compound at 2X final desired

concentration (using 4 microliter volume from a 1000X concentrated dilution series in 100 % DMSO); followed by 2,500 cells (using 100 microliters of 1x 10^4 cell /ml working stock), and finally 1 ml of 0.6 % agar stock at 37°C. Following careful mixing, 1 ml each is added to duplicate wells of the 12-well plate. The plate is then placed in a 37^0 C, 5% CO_2, humidified incubator for 10 to 14 days and read. Rapid diffusion of CPD throughout top and bottom agar layer results in final drug concentration of 1X.

[00150] Counting Colonies: After 10 days of incubation, the plates are removed from the incubator for photography and colony counting. Each well is scanned using an eyepiece with a micrometer guide and 5x phase optics. Colonies 50 micrometer or greater in diameter are scored as positive. Duplicate wells are averaged and percent inhibition calculated using number of colonies in no compound control wells as 100%.

[00151] All compounds described in Examples 1-3 were tested in accordance with the protocols of Examples 4-5 and determined to exhibit an IC_{50} value less than or equal to 25 micromolar.

Example 6. Inhibition of JAK Tyrosine Kinase and Tyrosine Kinase 2 Activity

[00152] Chemical entites as disclosed herein exhibit less than 50% inhibition of JAK Tyrosine Kinase and Tyrosine Kinase 2 when tested in the following assay. For screening purposes, compounds are diluted in 96 well plates at a concentration of 10 micromolar. Chemical entities are tested at a concentration of 1 micromolar. Plates are warmed at 37 °C for 30 minutes before assay.

[00153] JAK kinase domains are produced as follows:

JAK1

[00154] The kinase domain of humanJAK1 is amplified from U937mRNA using the polymerase chain reaction with the following primers:

XHOI-J1 5'-CCG CTC GAG ACT GAA GTG GAC CCC ACA CAT-3' (SEQ ID NO:2)

J1-KPNI 5'-CGG GOT ACC TTA TIT TAA AAG TGC TTC AAA-3' (SEQ ID NO:3)

JAK1 PCR products are cloned into the pFastBac HTb expression vector (Gitco) via the Xho I and Kpn I sites. The JAK1 plasmid is then transformed into competent DHlOBac cells (Gibco), and the recombinant baculovirus produced prepared for transfection into Sf9 insect cells.

JAK2

[00155] The kinase domain of human JAK2 is amplified from U937mRNA using the polymerase chain reaction with the following primers:

SALI-jk2 5'-ACG CGT CGA CGG TGC CTT TGA AGA CCG GGA T-3' (SEQ ID NO:4)
jk2-NOTI 5'-ATA GTT TAG CGG CCG CTC AGA ATG AAG GTC ATT T-3' JAK2 (SEQ ID NO:5)

PCR products are cloned into the pFastBac HTc expression vector (Gibco) via the Sal I and Not I sites. The JAK2 plasmid is then transformed into competent DHlOBac cells (Gitco), and the recombinant baculovirus produced prepared for transfection into Sf9 insect cells.

JAK3

[00156] The kinase domain of humanJAK3 is amplified from U937mRNA using the polymerase chain reaction with the following primers:

XHOI-J3 5'-CCG CTC GAG TAT GCC TGC CAA GAC CCC ACG-3' (SEQ ID NO:6)
J3-KPNI 5'-CGG GGT ACC CTA TGA AAA GGA CAG GGA GTG-3' (SEQ ID NO:7)

[00157] JAK3 PCR products are cloned into the pFastBac HTb expression vector (GiLco) via the Xho I and Kpn I sites. The JAK3 plasmid is then transformed into competent DHlOBac cells (Gibco), and the recombinant baculovirus produced prepared for transfection into Sf9 insect cells.

TYK2

[00158] The kinase domain of humanTYK2 is amplified from A549 mRNA using the polymerase chain reaction with the following primers:

HT2EK 5'-GGA GCA CTC GAG ATG GTA GCA CAC AAC CAG GTG-3' (SEQ ID NO:8)
ITY2.2R 5'-GGA GCA GGA ATT COG GCG CTG COG GTC AAA TCT GG-3' (SEQ ID NO:9)

TYK2 PCR products are cloned into pBlueBacHis2A (Invitrogen) via the EcoRI site. The recombinant TYK2 baculovirus produced is prepared for transfected into Sf9 insect cells.

Large Scale Production Of Kinase Domains

[00159] Baculovirus preparations from each of the JAK family members are infected into five litres of High Five cells (Invitrogen) grown in High Five serum free medium (Invitrogen) to a cell density of approximately 1-2 x 10^6 cells/ml.

[00160] Cells are infected with virus at a MOI of 0.8-3.0. Cells are harvested and lysed. JAK kinase domains are purified by affinity chromatography on a Probond (Invitrogen) nickel chelate affinity column.

Assay Protocols

[00161] Kinase assays are performed in a 96 well capture-based ELISA assay, using approximately 1.5 ug of affinity purified PTK domain in the presence of 50mM HEPES, pH 7.5, 10mM $MgCl_2$, 150mM NaCl and 10-20,uM ATP. The biotinylated substrate biotin-EGPWLEEEEEAYGWMDF-NH_2 (SEQ ID NO:10) (final 30

concentration HIM) is used as substrate, and tyrosine phosphorylation is quantitated following transfer to an avidin coated ELISA plate using peroxidase-linked anti-phospho-tyrosine antibody PY20.

[00162] Inhibitors are added to the assays fifteen minutes prior to the addition of ATP. Inhibitors are added in aqueous DMSO, with DMSO concentrations never exceeding 1%.

[00163] The cellular assays of Example 6 are performed as follows: Cell suspensions are prepared by harvesting cells from culture. Cell used in this test should be in later log phase growth and high viability. Cells are diluted in correct growth medium to 1.1X final concentration (from 50,000 5 cell/ml to 200, 000 cell/ml, depending on cell line). 90uL is added to samples, diluted in PBS to 10X final concentration in flat-bottom 96-well plates (DOLL). After incubation for 40 hr in 37 °C 5% CO_2 incubator, MTT 5mg/ml (in PBS, filter sterile) 20 ul per well is added. The plates are returned to incubator for another 6 hours. Lysis Buffer (10% SDS, 0.01N HCl) 100 ul per well is added and the plate put back in incubator overnight. The plate is then read at 590 nm.

Example 7. Btk Assays

[00164] A generalized procedure for one standard biochemical Btk Kinase Assay used to test compounds of formula 1 is as follows.

[00165] A master mix minus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer, 0.5 uM Promega PTK Biotinylated peptide substrate 2, and 0.01% BSA. A master mix plus Btk enzyme is prepared containing 1X Cell Signaling kinase buffer, 0.5 uM PTK Biotinylated peptide substrate 2, 0.01% BSA, and 100 ng/well (0.06 mU/well) BTK enzyme. A solution of 200 uM ATP is prepared. A quantity of 1.25 uL of compounds/DMSO is transferred to a 96-well ½ area Costar polystyrene plate. A quantity of 18.75 uL of master mix minus enzyme and master mix plus enzyme is transferred to appropriate wells in 96-well ½ area costar polystyrene plate. To that mixture is added 5 uL of 200 uM ATP to 96-well ½ area Costar polystyrene plate for final ATP concentration of 40 uM. The reaction is allowed to incubate for 1 hour at room temperature. The reaction is stopped with

Perkin Elmer 1X detection buffer containing 30 mM EDTA, 20 nM SA-APC, and 1 nM PT66 Ab. The plate is read using time-resolved fluorescence with a Perkin Elmer Envision using excitation filter 330 nm, emission filter 665 nm, and 2nd emission filter 615 nm. IC_{50} values are subsequently calculated.

[00166] Another generalized procedure for a standard cellular Btk Kinase Assay used to test compounds disclosed in this application is as follows.

[00167] Ramos cells are incubated at a density of $0.5x10^7$ cells/ml in the presence of test compound for 1 hr at 37 °C. Cells are then stimulated by incubating with 10 ug/ml anti-human IgM $F(ab)_2$ for 5 minutes at 37 °C. Cells are pelleted, lysed, and a protein assay is performed on the cleared lysate. Equal protein amounts of each sample are subject to SDS-PAGE and western blotting with either anti-phosphoBtk(Tyr223) antibody (Cell Signaling Technology #3531) to assess Btk autophosphorylation or an anti-Btk antibody (BD Transduction Labs #611116) to control for total amounts of Btk in each lysate.

Example 8. $EphB_4$ Assays.

[00168] The following is a general procedure for a standard biochemical assay for $EphB_4$ Kinase Activty

Materials:

[00169] 96-well, ½ area flat bottom, white polystyrene plates are purchased from Costar, cat #3693.

[00170] The cytoplasmic domain of recombinant $EphB_4$ kinase (amino acids 596-987, *Homo sapiens* $EphB_4$, GENBANK Accession No. AY056047.1) with a C-terminal 6X his tag is purified from Sf9 cells. Purity of >95% is assessed by Sypro-Ruby staining of SDS gels.

[00171] PTK Biotinylated Peptide Substrate 2, is purchased from Promega, cat #V288A; Lot # 740360.

[00172] LANCE Eu-W1024 labeled anti-phosphotyrosine antibody (PT66) is purchased from Perkin-Elmer, cat #AD0068; Lot #109144. Kinase Buffer is purchased from Cell Signaling cat #9802.

Method:

[00173] Dilutions of compounds are made in 100% DMSO at 20X the final desired concentration. Compounds in 100% DMSO are transferred (1.25 µL) to the 96 well assay plate. A 18.75 µL volume of master mix containing the final concentrations (in 25 ul) of 0.01% BSA, 1X Cell Signaling Kinase Buffer, 0.5 µM PTK Biotinylated Peptide Substrate 2, and 60 ng/well of $EphB_4$ kinase is added to all wells, except the four negative control wells (which contain no kinase), and mixed. To initiate the reaction, 5 µL of 550 uM ATP is added to each well. (Final Concentration of ATP = 110 µM). The reactions are incubated for 1 hour at room temperature (RT). After incubation a quantity of 8.35 µL of a 4X SA-APC Detection Mix is added to each well. The final concentration of Eu-labelled PT66 antibody is 1 nM and the SA-APC is 20 nM (based on the SA moiety). The reaction plates are incubated at RT for at least 15 minutes after SA-APC Detection Mix addition. The reaction plates are read on an Envision plate reader (Perkin-Elmer) with 605nm Excitation and 605nm and 640nm Emission wavelengths. Values are corrected for the fluorescence in the absence of enzyme and inhibition curves are fit to the data using a Logit curve-fitting algorithm. IC_{50} values are determined from these inhibition curves.

[00174] The following cell-based assay may also used to determine the effect of compounds on $EphB_4$ activity.

[00175] HEK293 cells stably expressing V5-epitope tagged $EphB_4$ are grown to ~75% confluency, and then incubated for 1 hr at 37 °C in low serum media (Optimem) containing test compound. Cells are stimulated for 10 minutes at 37 °C with 500ng/ml $EphrinB_2$/Fc chimera and 50ng/ml goat-anti-human IgG (FC specific) in low serum media containing test compound. Cells are washed in ice-cold PBS, lysed, and protein assays are performed on the cleared lysates. Equal protein amounts of each sample are subjected to SDS-PAGE and western blotting with either an anti-phosphotyrosine antibody or an anti-V5 antibody to control for total amounts of v5-tagged $EphB_4$ in each lysate.

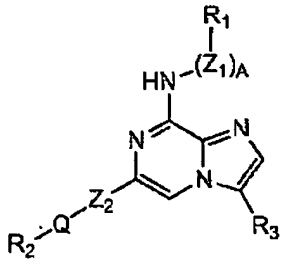
[00176] Chemical entities disclosed herein are tested in the biochemical and cellular assay of Example 7 and are determined to exhibit an IC_{50} value less than or

equal to 1 micromolar in the biochemical assay and 10 micromolar in the cellular assay. In another embodiment, chemical entities are tested in the biochemical and cellular assay of Example 8 and are determined to exhibit an IC_{50} value less than or equal to 1 micromolar in the biochemical assay and 10 micromolar in the cellular assay.

[00177] While some embodiments have been shown and described, various modifications and substitutions may be made thereto without departing from the spirit and scope of the invention. Accordingly, it is to be understood that the present invention has been described by way of illustration and not limitations.

What is claimed is:

1. At least one chemical entity chosen from compounds of Formula I:

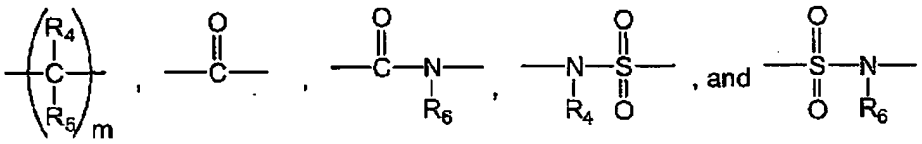


(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo;

m is chosen from 0, 1, 2, and 3; and

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl).

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

pyridylidene,

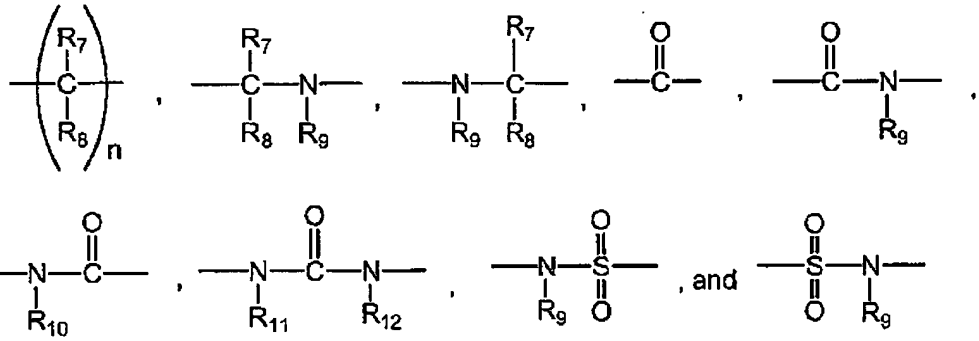
substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy,

nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo;

n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-

(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl.

2. At least one chemical entity of claim 1 wherein R_2-Q- is halo-C_1-C_4 alkyl.

3. At least one chemical entity of claim 1 wherein R_2-Q- is chosen from phenoxy and

substituted phenoxy chosen from mono-, di-, and tri-substituted phenoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

4. At least one chemical entity of claim 1 wherein

R_6 is chosen from hydrogen, C_1-C_6 alkyl, and phenyl;

R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano,

carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl,

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyrimidinyl, and

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyrimidinyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6

alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

R_2-Q- is chosen from

chloro-C_1-C_4 alkyl,

phenoxy, and

substituted phenoxy chosen from mono-, di-, and tri-substituted phenoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4alkyl).

5. At least one chemical entity of claim 1 wherein

R_6 is chosen from hydrogen, C_1-C_6 alkyl, and phenyl;

R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl,

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyrimidinyl, and

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyrimidinyl wherein the substituents are independently chosen from

hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Z_2 is chosen from

substituted phenylene chosen from mono-, di-, and tri-substituted phenylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

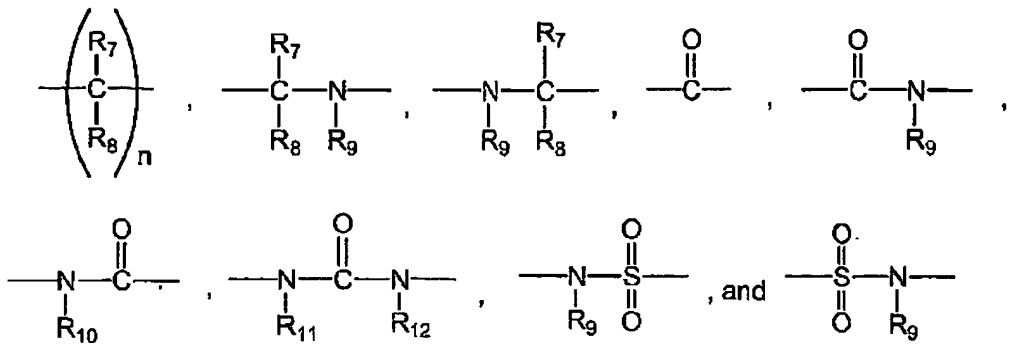
pyridylidene,

substituted pyridylidene chosen from mono-, di-, and tri-substituted pyridylidene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl),

and

substituted naphthylidene chosen from mono-, di-, and tri-substituted naphthylene with substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo, and n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from hydrogen, C_1-C_6 alkyl, and phenyl;

R_2 is chosen from

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

(C_3-C_7 cycloalkyl)methyl,

substituted (C_3-C_7 cycloalkyl)methyl chosen from mono-, di-, and tri-substituted (C_3-C_7 cycloalkyl)methyl wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents

are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

(heterocycloalkyl)C_1-C_2 alkyl,

substituted (heterocycloalkyl)C_1-C_2 alkyl chosen from mono-, di-, and tri-substituted (heterocycloalkyl)C_1-C_2 alkyl, wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, cyano, amino, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_4 alkyl)amino, and di-(C_1-C_4 alkyl)amino,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

pyridyl,

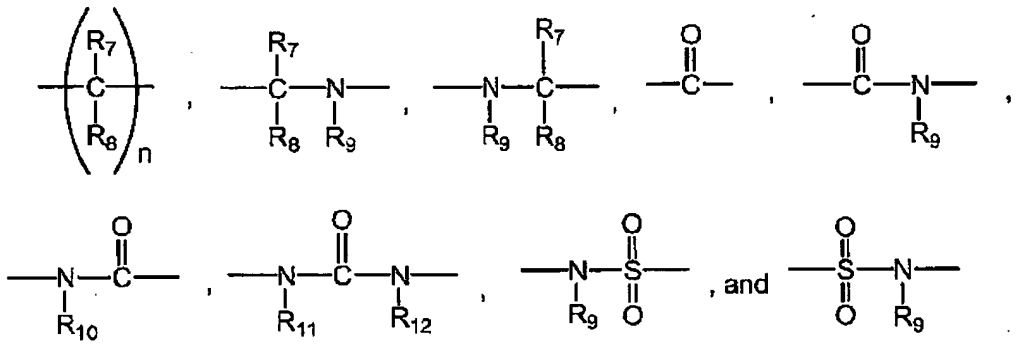
substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

pyrimidinyl, and

substituted pyrimidinyl chosen from mono-, di-, and tri-substituted pyrimidinyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6

alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

6. At least one chemical entity of claim 1 or 5 wherein Q is chosen from

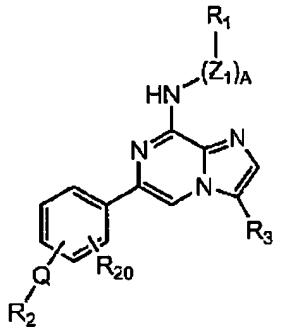


wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo; and n is chosen from 1 and 2; and

R_9-R_{12} are each independently chosen from hydrogen, C_1-C_6 alkyl, and phenyl.

7. At least one chemical entity chosen from compounds of Formula 2:



(Formula 2)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

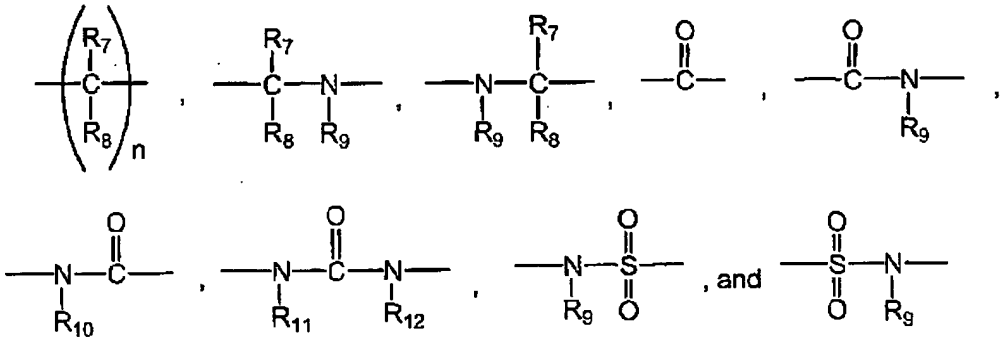
substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino,

sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo; and n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6

haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

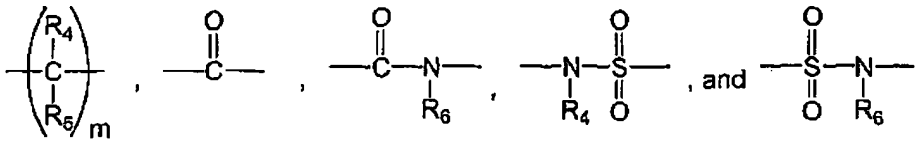
substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

A is chosen from 0 and 1; and

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

8. At least one chemical entity of claim 7 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

9. At least one chemical entity of any of claims 7 or 8 wherein R_1 is chosen from phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy,

amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

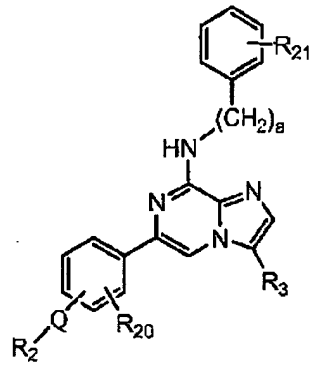
benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

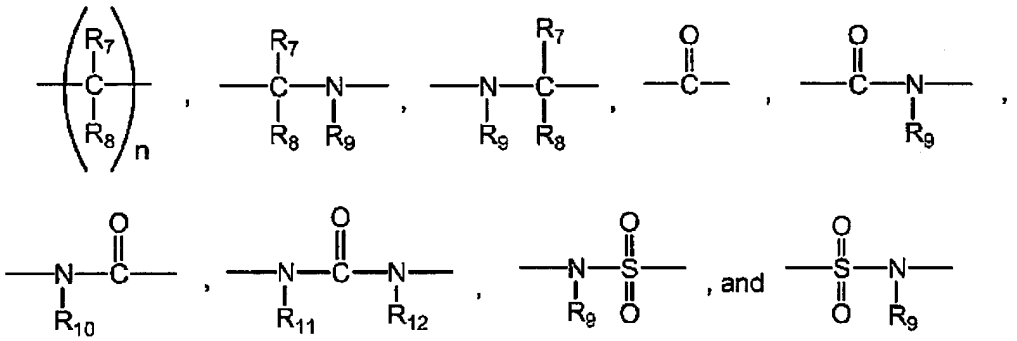
10. At least one chemical entity chosen from compounds of Formula 3



(Formula 3)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

Q is chosen from



wherein

each occurrence of R_7 and R_8 is independently chosen from C_1-C_6 alkyl, sulfonamido, and halo; and n is chosen from 0, 1, 2, and 3; and

R_9-R_{12} are each independently chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, halo, C_1-C_6 alkyl, C_1-C_6

alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_1-C_6 alkyloxy)C_1-C_6 alkoxy, C_1-C_6 perfluoroalkyl, C_1-C_6 perfluoroalkoxy, mono-(C_1-C_6 alkyl)amino, di(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

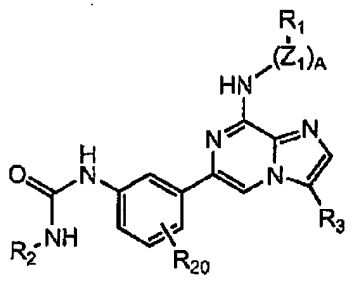
a is chosen from 0, 1, 2 and 3;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl); and

R_{21} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6alkoxycarbonyl.

11. At least one chemical entity of claim 10 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

12. At least one chemical entity chosen from compounds of Formula 4



(Formula 4)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano,

carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_2 is chosen from

C_1-C_7 alkyl,

substituted C_1-C_7 alkyl chosen from mono-, di-, and tri-substituted C_1-C_7 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-

C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

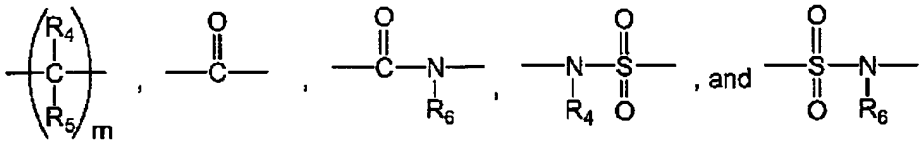
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

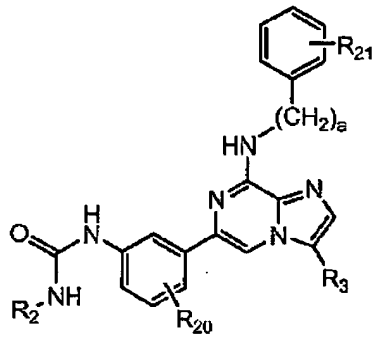
substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl); and

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-

C_6alkoxy, mono-(C_1-C_4alkyl)amino, di-(C_1-C_4alkyl)amino, and amino(C_1-C_4 alkyl).

13. At least one chemical entity of claim 12 wherein R_{20} represents 1 substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

14. At least one chemical entity chosen from compounds of Formula 5



(Formula 5)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

a is chosen from 0, 1, 2 and 3;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

R_2 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are indepedently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6

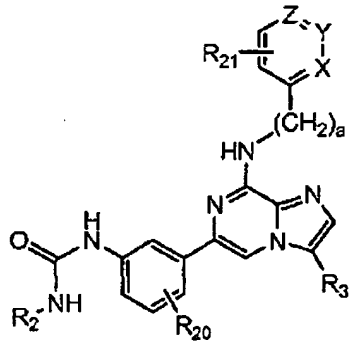
alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are indepedently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl.

15. At least one chemical entity of claim 14 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

16. At least one chemical entity chosen from compounds of Formula 6



(Formula 6)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

a is chosen from 0, 1, 2 and 3;

X, Y, and Z are chosen from nitrogen and CH, wherein one and only one of X, Y, and Z is nitrogen;

R_{21} represents 0 to 4 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6

haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl alkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl,

C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7

cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl.

17. At least one chemical entity of claim 16 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

18. At least one chemical entity of any of claims 16 or 17 wherein

R_2 is chosen from

phenyl,

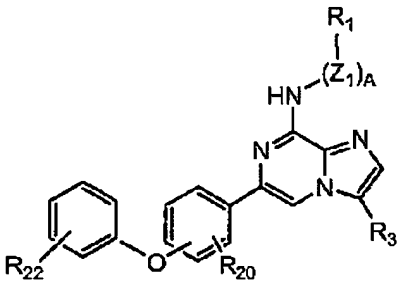
substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2

haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl.

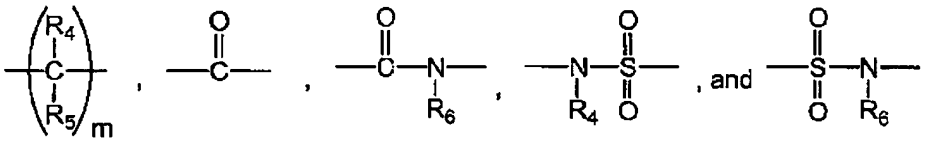
19. At least one chemical entity chosen from compounds of Formula 7



(Formula 7)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof wherein

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-

C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

A is chosen from 0 and 1; and

R_1 is chosen from

C_3-C_7 cycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

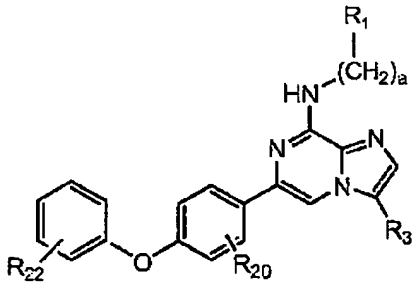
substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl); and

R_{22} represents 0 to 4 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

20. At least one chemical entity of claim 19 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

21. At least one chemical entity chosen from compounds of Formula 8



(Formula 8)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro,

cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

R_{22} represents 0 to 4 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

R_1 is chosen from

C_3-C_7 cycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

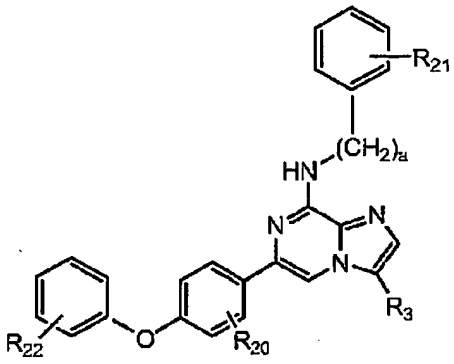
pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl; and

a is chosen from 0 and 1.

22. At least one chemical entity of claim 21 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

23. At least one chemical entity chosen from compounds of Formula 9



(Formula 9)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

R_{22} represents 0 to 4 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

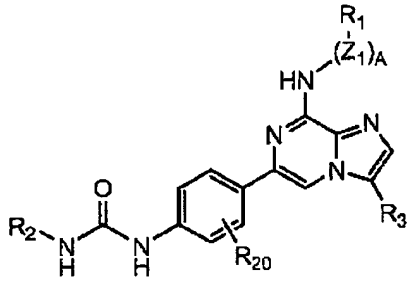
a is chosen from 0 and 1; and

R_{21} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6

alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

24. At least one chemical entity of claim 23 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

25. At least one chemical entity chosen from compounds of Formula 10



(Formula 10)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

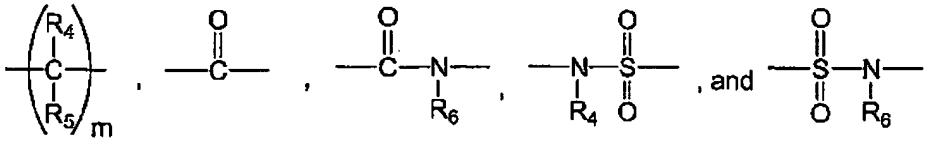
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl);

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl); and

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl alkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-

C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

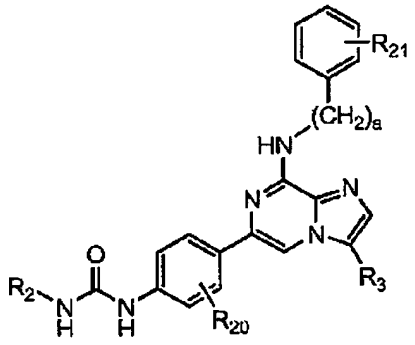
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

26. At least one chemical entity of claim 25 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

27. At least one chemical entity chosen from compounds of Formula 11



(Formula 11)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl alkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

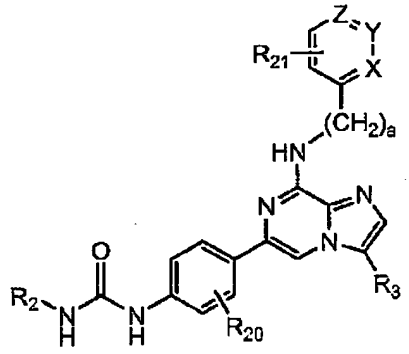
a is chosen from 0, 1, 2, and 3; and

R_{21} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6

haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

28. At least one chemical entity of claim 27 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

29. At least one chemical entity chosen from compounds of Formula 12



(Formula 12)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

a is chosen from 0, 1, 2, and 3;

X, Y, and Z are chosen from nitrogen and CH, wherein one and only one of X, Y, and Z is nitrogen;

R_2 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl,

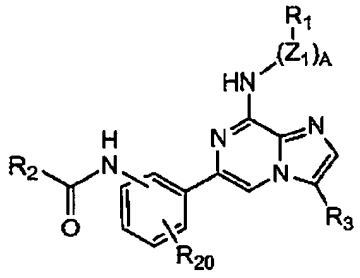
pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl; and

R_{21} represents 0 to 4 substituents independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6alkoxycarbonyl.

30. At least one chemical entity of claim 29 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

31. At least one chemical entity chosen from compounds of Formula 13



(Formula 13)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

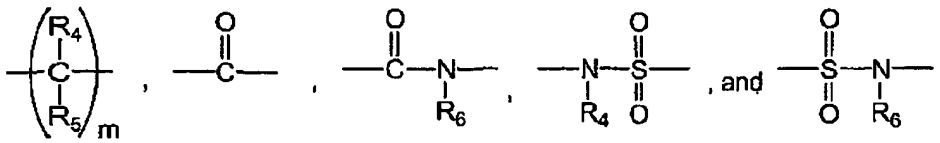
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl.

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

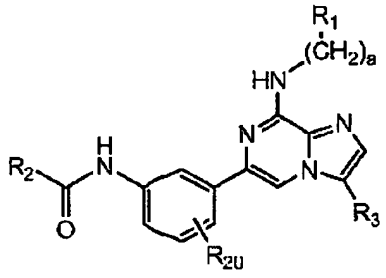
32. At least one chemical entity of claim 31 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

33. At least one chemical entity of any of claims 31 or 32 wherein R_2 is chosen from

phenyl substituted with at least one branched C_3-C_6alkyl, and further substituted with 0 to 2 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl, and

pyridyl substituted with at least one branched C_3-C_6alkyl, and further substituted with 0 to 2 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, piperidinyl, piperazinyl, and morpholinyl.

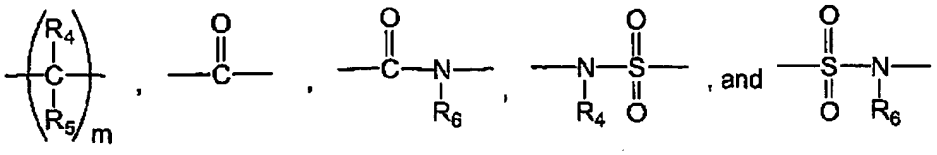
34. At least one chemical entity chosen from compounds of Formula 14



(Formula 14)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl.

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl); and

a is chosen from 0 and 1.

35. At least one chemical entity of claim 34 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

36. At least one chemical entity of any of claims 34 or 35 wherein R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6

alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6 alkoxycarbonyl,

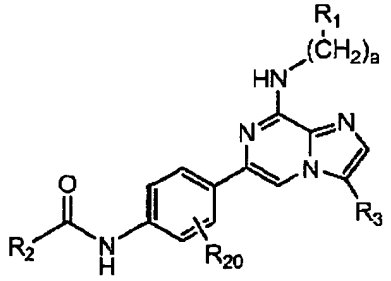
benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6alkanoyl, and C_1-C_6 alkoxycarbonyl.

37. At least one chemical entity chosen from compounds of Formula 15



(Formula 15)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-

C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_1 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl.

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl);

a is chosen from 0 and 1.

38. At least one chemical entity of claim 37 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

39. At least one chemical entity of any one of claims 37 or 38 wherein, R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

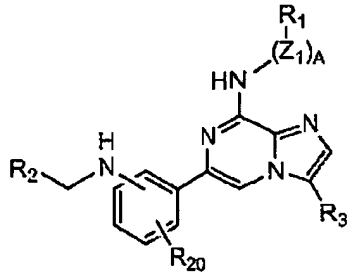
benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

40. At least one chemical entity chosen from compounds of Formula 16



(Formula 16)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino,

sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

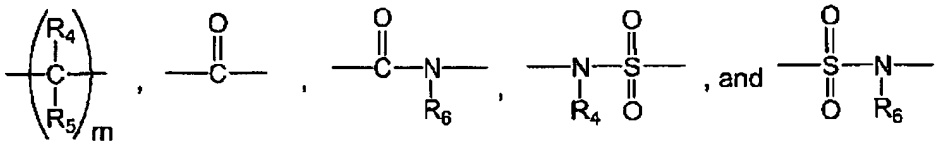
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

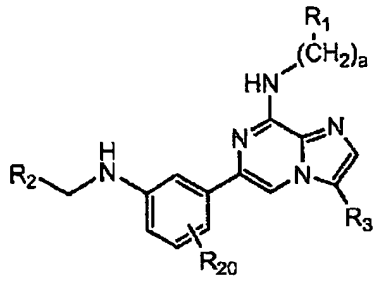
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4alkyl).

41. At least one chemical entity of claim 40 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

42. At least one chemical entity chosen from compounds of Formula 17



(Formula 17)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-

C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4alkyl); and

a is chosen from 0 and 1.

43. At least one chemical entity of claim 42 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

44. At least one chemical entity of any one of 42 or 43 wherein R_1 is chosen from phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

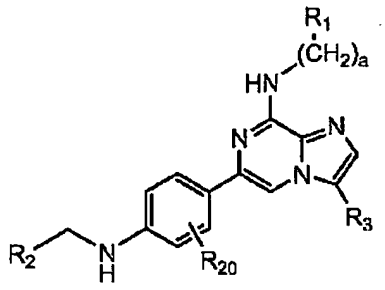
benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

45. At least one chemical entity chosen from compounds of Formula 18



(Formula 18)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-

C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl;

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4alkyl); and

a is chosen from 0 and 1.

46. At least one chemical entity of claim 45 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

47. At least one chemical entity of any one of claims 44 or 45 wherein R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

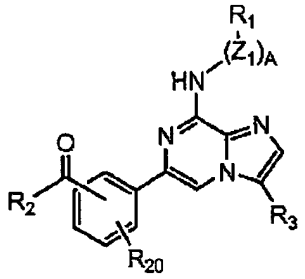
benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

48. At least one chemical entity chosen from compounds of Formula 19



(Formula 19)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or hetcroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

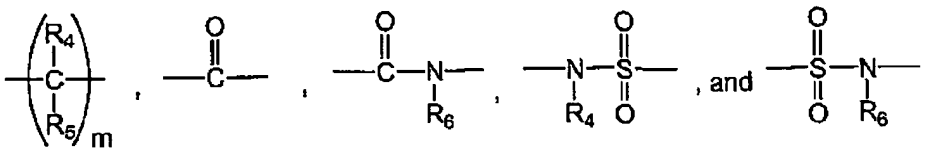
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

A is chosen from 0 and 1;

Z_1 is chosen from



wherein

each occurrence of R_4 and R_5 is independently chosen from hydrogen, C_1-C_6 alkyl, sulfonamido, and halo, and m is chosen from 0, 1, 2, and 3;

R_6 is chosen from

hydrogen,

C_1-C_6 alkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl),

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substitutents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, and amino(C_1-C_6 alkyl);

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-

C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

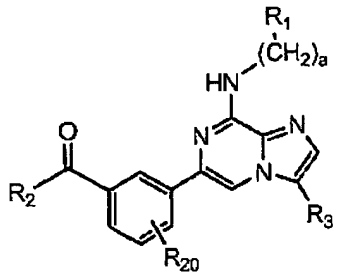
heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

49. At least one chemical entity of claim 48 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

50. At least one chemical entity chosen from compounds of Formula 20



(Formula 20)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano,

carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6

haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-

C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl); and

a is chosen from 0 and 1.

51. At least one chemical entity of claim 50 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

52. At least one chemical entity of any one of claims 50 or 51 wherein R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6alkoxycarbonyl,

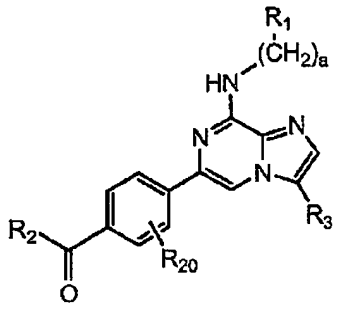
benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6alkox

53. At least one chemical entity chosen from compounds of Formula 21



(Formula 21)

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof, wherein

R_1 is chosen from

hydrogen,

C_1-C_7 alkyl,

C_1-C_6 alkoxy,

C_3-C_7 cycloalkyl,

(C_3-C_7 cycloalkyl)methyl,

heterocycloalkyl,

(heterocycloalkyl)C_1-C_2 alkyl,

sulfonamido,

(C_1-C_6 alkoxy)C_1-C_6 alkoxy,

mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino,

mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl),

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S,

substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, chosen from mono-, di-, and tri-substituted phenyl fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or 2 heteroatoms chosen from N, O, and S, or heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl, wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl;

R_3 is chosen from hydrogen, C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, heterocycloalkyl, and (heterocycloalkyl)C_1-C_2 alkyl;

R_2 is chosen from

C_1-C_6 alkyl,

substituted C_1-C_6 alkyl chosen from mono-, di-, and tri-substituted C_1-C_6 alkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_3-C_7 cycloalkyl,

substituted C_3-C_7 cycloalkyl chosen from mono-, di-, and tri-substituted C_3-C_7 cycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heterocycloalkyl,

substituted heterocycloalkyl chosen from mono-, di-, and tri-substituted heterocycloalkyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

C_1-C_6 alkoxy,

substituted C_1-C_6 alkoxy chosen from mono-, di-, and tri-substituted C_1-C_6 alkoxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

aryloxy,

substituted aryloxy chosen from mono-, di-, and tri-substituted aryloxy wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl,

heteroaryl, and

substituted heteroaryl chosen from mono-, di-, and tri-substituted heteroaryl wherein the substituents are independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, (C_1-C_6 alkoxy)C_1-C_6 alkoxy, mono-(C_1-C_6 alkyl)amino,

di-(C_1-C_6 alkyl)amino, amino(C_1-C_6 alkyl), C_1-C_6 alkylthio, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, C_2-C_6 alkanoyl, C_1-C_6 alkoxycarbonyl, and heterocycloalkyl; and

R_{20} represents 1, 2, or 3 substituents independently chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl); and

a is chosen from 0 and 1.

54. At least one chemical entity of claim 53 wherein R_{20} represents one substituent chosen from hydroxy, nitro, cyano, amino, halo, C_1-C_6 alkyl, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_6 alkoxy, mono-(C_1-C_4 alkyl)amino, di-(C_1-C_4 alkyl)amino, and amino(C_1-C_4 alkyl).

55. At least one chemical entity of any one of claims 53 or 54 wherein R_1 is chosen from

phenyl,

substituted phenyl chosen from mono-, di-, and tri-substituted phenyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

benzo[*d*]1,3-dioxolyl,

substituted benzo[*d*]1,3-dioxolyl chosen from mono-, di-, and tri-substituted benzo[*d*]1,3-dioxolyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6

alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl,

pyridyl, and

substituted pyridyl chosen from mono-, di-, and tri-substituted pyridyl wherein the substituents are independently chosen from hydroxy, nitro, cyano, carboxy, amino, sulfonamido, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, mono-(C_1-C_6 alkyl)amino, di-(C_1-C_6 alkyl)amino, mono-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), di-(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), C_2-C_6 alkanoyl, and C_1-C_6 alkoxycarbonyl.

56. At least one chemical entity of claim 1 chosen from

4-{6-[3-(4-tert-Butyl-benzoylamino)-4-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-{6-[5-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid;

4-{6-[3-(4-tert-Butyl-benzoylamino)-2-methyl-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester;

4-tert-Butyl-N-{2-methyl-5-[8-(4-sulfamoyl-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide;

and pharmaceutically acceptable salts, solvates, crystal forms, diastereomers, and prodrugs thereof.

57. At least one chemical entity according to any one of claims 1 to 56, wherein in an in vitro assay of kinase modulation, the at least one chemical entity exhibits an IC_{50} value less than or equal to 25 micromolar.

58. At least one chemical entity according to any one of claims 1 to 57, wherein in an in vitro assay of modulation of soft agar growth, the at least one chemical entity exhibits a IC_{50} value less than or equal to 25 micromolar.

59. At least one chemical entity according to any one of claims 1 to 58, wherein in an in vitro assay of modulation of cell growth in soft agar, the at least one chemical entity exhibits an IC_{50} value less than or equal to 25 micromolar, wherein the cells are chosen from HCT-15, MiaPaca-2, MCF-7, OVCAR-4, and A549 cells, the at least one chemical entity exhibits an IC_{50} value less than or equal to 25 micromolar.

60. A pharmaceutical composition comprising at least one chemical entity according to any one of claims 1 to 59; and at least one pharmaceutically acceptable carrier or excipient.

61. A method of treating a kinase-implicated condition in a mammal having a kinase-implicated condition, comprising administering to the mammal a therapeutically effective amount of at least one chemical entity of any one of claims 1 to 59.

62. The method of claim 61, wherein the mammal is a human.

63. The method of claim 61, wherein the mammal is a dog or cat.

64. A method of treating cancer, comprising administering to a mammal in need thereof a therapeutically effective amount of at least one chemical entity according to any one of claims 1 to 59.

65. A method of treating cancer, comprising administering to a mammal in need thereof a therapeutically effective amount of at least one chemical entity according to any one of claims 1 to 59 and a therapeutically effective amount of at least one antitumor therapeutic.

66. The method of claim 65, wherein treatment with the at least one antitumor therapeutic follows treatment with the at least one chemical entity of any one of claims 1 to 85.

67. The method of claim 65, wherein the at least one antitumor therapeutic is at least one other chemotherapeutic agent.

68. The method of claim 67, wherein the at least one chemotherapeutic agent is chosen from mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, and doxorubicin.

69. The method of claim 65, wherein the at least one antitumor therapeutic is at least one radiotherapeutic agent.

70. The method of Claim c5, wherein the mammal is a human.

71. The method of claim 65, wherein the mammal is a dog or cat.

72. A method for identifying a kinase, comprising contacting an organism, cell, or preparation comprising the kinase with at least one chemical entity according to claims 1 to 59, and detecting modulation of an activity of a kinase, whereby the kinase is identified.

73. A method of treating a Btk-implicated condition in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one chemical entity according to claims 1 to 59.

74. The method of claim 73 wherein an additional kinase is implicated in the condition.

75. The method of claim 73 wherein the mammal is a human.

76. The method of claim 73 wherein the mammal is a dog or cat.

77. A method for identifying Btk, comprising

contacting an organism, cell, or preparation comprising the kinase with at least one chemical entity according to Claims 1 to 59, whereby

detecting modulation of an activity of Btk, whereby Btk is identified.

78. A method of treating a Btk-implicated autoimmune/inflammatory condition in a mammal, comprising administering to the mammal a therapeutically effective amount of at least one chemical entity according to claims 1 to 59.

79. The method of claim 78, wherein the mammal is a human.

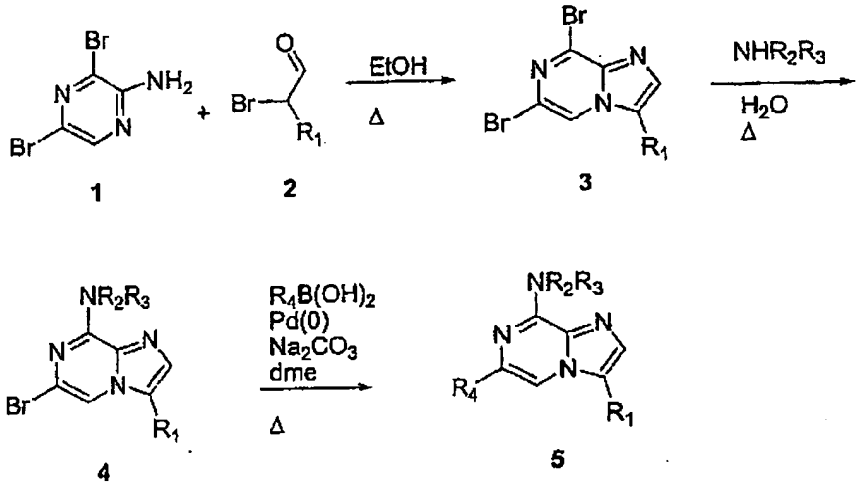
80. The method of claim 78 wherein the mammal is a dog or cat.

81. The use of a compound for the manufacture of a medicament for the treatment of a patient having a disease or disorder responsive to activity modulation of Btk, wherein said compound is at least one chemical entity according to claims 1 to 59.

82. The use of claim 81 wherein the disease or disorder responsive to activity modulation of Btk is cancer.

83. The use of claim 81 wherein the disease or disorder responsive to activity modulation of Btk is an autoimmune and/or inflammatory condition.

FIGURE 1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N
N
Br
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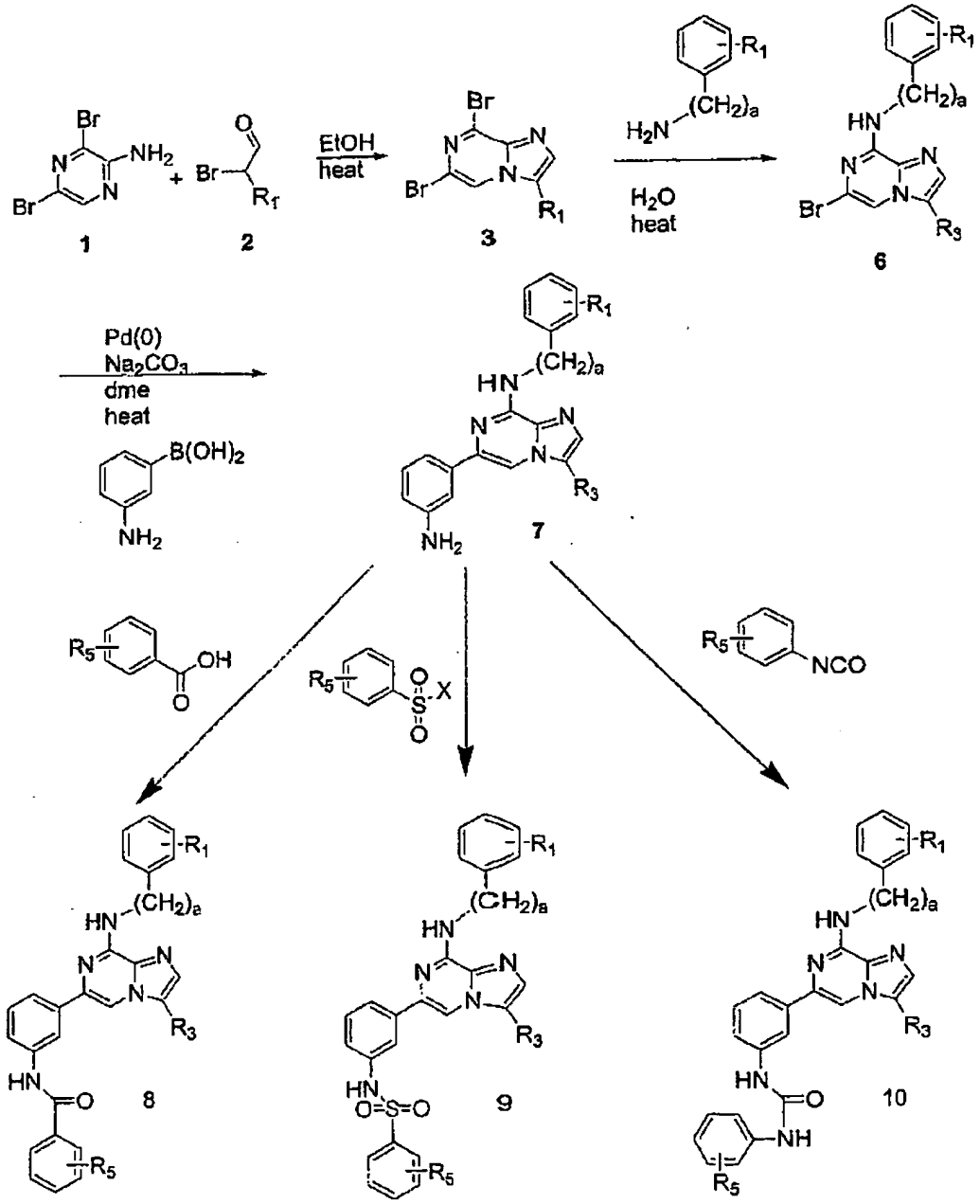
FIGURE 2



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Pippin, Douglas A.
Darrow, James W.
Mitchell, Scott A.

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